CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are At Risk of HIV-1 Infection	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number: **EudraCT Number:**	127728 2016-001399-31	
Indication:	Pre-Exposure Prophylaxis of HIV-1 Infection	
Protocol ID:	GS-US-412-2055	
Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
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Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3: Amendment 4: Amendment 5:	07 April 2016 06 June 2016 15 July 2016 16 November 2016 06 April 2018 05 September 2018

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are At Risk of HIV-1 Infection
IND Number:	127728
EudraCT Number:	2016-001399-31
Study Centers Planned:	Approximately 100 centers in North America and Europe
Objectives:	The primary objective of this study is: • To assess the rates of HIV-1 infection in men (MSM) and transgender women (TGW) who have sex with men who are administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization The secondary objectives of this study are: • To compare bone safety between the treatments as determined by dual energy x-ray absorptiometry (DXA) tests of hip and spine bone mineral density (BMD) in a subset of participants at Week 48 and Week 96 in the blinded phase • To compare renal safety between the treatments as determined by urine retinol-binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, urine protein to creatinine ratio (UPCR), and serum creatinine at Week 48 and Week 96 in the blinded phase • To assess the rates of HIV-1 infection in men (MSM) and transgender women (TGW) who have sex with men who are administered daily F/TAF or F/TDF when all subjects have 96 weeks of follow-up after randomization • To compare the general safety between the treatments

Exploratory objectives of this study include:

[redacted]

Study Design:

Randomized, double-blind comparison of the safety and efficacy of F/TAF versus F/TDF administered orally once daily (QD).

All subjects must meet eligibility criteria in order to receive treatment in the study. Once randomized to receive treatment in the study, all subjects must return to the study center for required visits at Weeks 4, 12, and then every 12 weeks thereafter.

All subjects will remain blinded to study treatment for at least 96 weeks. The primary endpoint data will be collected and analyzed after all subjects have a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization.

Once all subjects have at least 96 weeks of follow-up after randomization and upon notification by Gilead, all subjects will return to the study center for an End of Blinded Treatment Phase visit (may coincide with their next scheduled visit).

Subjects who are still on blinded study drug at the end of Blinded Treatment Phase visit will be offered entry into the 48 week open-label extension (OL phase) of the study. Subjects who continue participation in the OL phase will be administered F/TAF QD and will return to the study center for visits at OL Weeks 12, 24, 36, and 48.

Subjects who have discontinued study drug prior to the End of Blinded Treatment Phase visit due to HIV infection will be eligible to continue participation in the OL phase, but will not be administered F/TAF QD. Subjects who have discontinued study drug for any other reason prior to the End of Blinded Treatment Phase visit will not be eligible to participate in the OL Phase.

	DXA scans will be performed during regular intervals throughout the study in a subset of approximately 400 subjects at a subset of sites (excluding Germany).
Number of Subjects Planned:	5000
Target Population:	MSM and TGW (male at birth) who are at risk of HIV-1 infection through sexual exposure with other men
Duration of Treatment:	**Blinded Phase:** Subjects will receive study drug for at least 96 weeks. After completing the Week 96 visit, all subjects will continue to take their blinded study drug and attend visits every 12 weeks until the last subject reaches Week 96. All subjects will return to the study center for an End of Blinded Treatment Phase visit (may coincide with their next scheduled visit) upon notification by Gilead. Subjects who are still on study drug and subjects who have discontinued study drug due to HIV infection at the End of Blinded Treatment Phase visit will be offered the option to continue participation in the OL phase of the study. **Open-Label Phase:** Subjects will receive OL F/TAF for 48 weeks. HIV infected subjects may continue participation in the OL phase but will not be offered OL F/TAF. In geographic regions where F/TAF is commercially available for PrEP, subjects will discontinue study drug at OL Week 48 and return 30 days later for a 30 Day Follow-Up visit. In geographic regions where F/TAF is not yet commercially available for PrEP, subjects will be given the option to continue receiving OL F/TAF beyond OL Week 48 and attend visits every 12 weeks until F/TAF becomes commercially available for use as PrEP, or until Gilead Sciences terminates the clinical development of F/TAF for PrEP (except in Denmark and the United Kingdom).

Diagnosis and Main Eligibility Criteria:

- HIV-1 negative status
- MSM or TGW (male at birth) who have at least one of the following:
  a) condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)
  b) documented history of syphilis in the past 24 weeks
  c) documented history of rectal gonorrhea or chlamydia in the past 24 weeks
- Age ≥ 18 years
- No suspected or known active, serious infection(s)
- Estimated glomerular filtration rate ≥ 60 mL/min according to the Cockcroft-Gault formula
- Adequate liver and hematologic function:
- AST and ALT ≤ 2.5 × upper limit of normal (ULN) and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin
- Absolute neutrophil count ≥ 1000/mm^3; platelets ≥ 75,000/mm^3; hemoglobin ≥ 10 g/dL
- Have not received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening
- No evidence of acute viral hepatitis A, B or C, and no evidence of chronic hepatitis B virus infection. Subjects found to be susceptible to HBV infection should be referred for HBV vaccination. Subjects found to be positive for HCV must not have active infection or must have completed treatment and achieved a sustained virologic response
- No history of osteoporosis or bone fragility fractures

Study Procedures/ Frequency:

Screening Visit

Upon providing written informed consent, subjects will be evaluated for eligibility at the Screening visit, including medical history review, concomitant medication review, complete physical examination including height, weight, and vital signs, sexually transmitted infection (STI) testing for gonorrhea, chlamydia, and syphilis, 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test, HIV Ab/Ag testing, HIV-1 RNA testing if applicable, Hepatitis B testing, Hepatitis C testing, clinical laboratory assessments for blood and urine samples, computer-assisted self-interview (CASI) for: recent sexual risk

events; interest in using PrEP; self-identification of transgender status; education and employment history; and use of tobacco and recreational drugs, and risk reduction counseling including provision of condoms.

Prior to the Day 1 visit and randomization, the investigator will review the Screening assessments to confirm eligibility. The Day 1 visit must occur within 30 days after the Screening visit.

Blinded Treatment Phase

During the blinded treatment phase, subjects will be seen at the study center for visits at Day 1, Weeks 4, 12, 24, and every 12 weeks thereafter until the End of Blinded Treatment Phase visit.

At the Day 1 visit, subjects will be assessed with 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test, HIV-1 RNA if applicable, adverse event (AE) and concomitant medication review, targeted physical examination and vital signs if applicable, CASI, and adherence and risk reduction counseling including provision of condoms. Subjects participating in the DXA substudy will also have DXA scans of the hip and spine performed.

At all other study visits during the blinded treatment phase, subjects will be assessed with targeted physical examination (complete physical examination at Week 48 and 96), AE and concomitant medication review, vital signs if clinically indicated, weight, STI testing for gonorrhea, chlamydia, and syphilis, 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test, HIV Ag/Ab testing, HIV-1 RNA testing if applicable, Hepatitis B testing (every 24 weeks), Hepatitis C testing (every 48 weeks), clinical laboratory assessments for blood and urine samples, CCI [redacted], PK sample collection (trough PK blood and PBMC at Week 4 only, anytime PK blood sample at all other visits), dried blood spot (DBS) collection, CASI, adherence and risk reduction counseling including provision of condoms. Subjects participating in the DXA substudy will have DXA scans of the hip and spine at Weeks 48 and 96.

If the subject discontinues study drug prior to the End of Blinded Treatment Phase visit, the subject will be asked to return to the study center within 72 hours of stopping study drug for the Early Study Drug Discontinuation (ESDD) visit. The subject will be asked to continue attending the scheduled study visits through the end of the blinded treatment phase of the study. Subjects participating in the DXA substudy will have DXA scans of the hip and spine at the ESDD visit (if ESDD visit is more than 12 weeks from the prior DXA scan).

	Subjects who are still on study drug at the End of Blinded Treatment Phase visit will be offered entry into the 48 week OL phase of the study. Subjects who have discontinued study drug prior to the end of Blinded Treatment Phase visit due to HIV infection will be eligible to continue participation in the OL phase, but will not be administered F/TAF QD. **Open-Label Phase** During the OL phase, subjects will be seen at the study center for visits at OL Weeks 12, 24, 36, and 48. At all study visits during the OL phase, subjects will be assessed with targeted physical examination (complete physical examination at OL Week 48), AE and concomitant medication review, vital signs if clinically indicated, weight, STI testing for gonorrhea, chlamydia, and syphilis, 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test, HIV Ab/Ag testing, HIV-1 RNA testing if applicable, Hepatitis B testing (every 24 weeks), Hepatitis C testing (every 48 weeks), clinical laboratory assessments for blood and urine samples, plasma storage sample collection, anytime PK blood sample, DBS collection, CASI, adherence and risk reduction counseling including provision of condoms. Subjects participating in the DXA substudy will have DXA scans of the hip and spine at OL Week 48. Throughout the study, subjects may be asked to provide daily information on adherence and sexual risk events through the use of a diary. Participants may also receive periodic contacts to remind them to take their study drug and to provide any additional support needed.
Test Product, Dose, and Mode of Administration:	**Blinded Phase:** F/TAF fixed-dose combination (200 mg emtricitabine/25 mg tenofovir alafenamide), administered orally once daily (QD). **Open-Label Phase:** F/TAF fixed-dose combination (200 mg emtricitabine/25 mg tenofovir alafenamide), administered orally QD.
Reference Product, Dose, and Mode of Administration:	**Blinded Phase:** F/TDF fixed-dose combination (200 mg emtricitabine/300 mg tenofovir disoproxil fumarate), administered orally QD.

Criteria for Evaluation:

Safety:	Adverse events, physical examinations, vital signs Clinical laboratory tests of blood and urine DXA scan (DXA substudy participants only) STI testing Adherence measures including tablet collection, responses to adherence questions as part of the CASI, and FTC and/or TFV levels in the plasma or DBS
Efficacy:	Incidence of HIV-1 infection defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab: 1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by the reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated subjects, or 2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or 3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results) Please refer to Appendix 6 for more details.
Pharmacokinetics:	Plasma samples will be collected at all study visits to evaluate the PK of plasma concentrations of TFV and/or FTC. A single pre-dose PBMC sample will be collected at the Week 4 visit to evaluate the intracellular concentrations of TFV-DP and FTC-TP.
Risk Behavior Assessment:	Computer-Assisted Self-Interview (CASI) sexual risk event evaluation
Statistical Methods:	The primary endpoint will be the incidence of HIV-1 infection (as defined above) per 100 person years (PY). The primary analysis will occur when all subjects have a minimum of 48 weeks of follow-up and at least 50% of the subjects have at least 96 weeks of follow-up after randomization. The primary analysis will consist of a non-inferiority evaluation of F/TAF versus F/TDF, with respect to the HIV-1 infection rate in PY as determined by rate ratios. It will be concluded that F/TAF is non-inferior to F/TDF if the upper bound of the 95% confidence interval of the ratio between the two arms (F/TAF over F/TDF) is less than 1.62. The 95% confidence interval will be constructed

using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the covariate. A sample size of 2500 in each arm provides at least 82% power to show F/TAF is non-inferior to F/TDF with respect to the HIV-1 infection rate, and assumes an HIV-1 infection rate of 1.44 per 100 PY in the F/TAF and F/TDF treatment arms, a 2-sided Type 1 error rate of 5%, and an average follow-up of 2 years (i.e., last subject has a minimum of 48 weeks of follow-up and at least 50% of the subjects have at least 96 weeks of follow-up after randomization).

An independent data monitoring committee (IDMC) will be convened to primarily evaluate the safety of the treatments in this population. There are no a priori plans to stop for efficacy or futility with formal boundaries. At a minimum, the IDMC will include two clinicians (including a chair person), a biostatistician, a prevention expert, and a community member. The initial evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 24 (or prematurely discontinued from the study drug) or (2) after 50 HIV-1 infections have been reported, whichever occurs earlier. The second evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 48 (or prematurely discontinued from the study drug) or (2) after 100 HIV-1 infections have been reported, whichever occurs earlier. The third evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 72 (or prematurely discontinued from the study drug) or (2) after 150 HIV-1 infections have been reported, whichever occurs earlier.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANOVA	analysis of variance
ARV	antiretroviral
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0\text{-}last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last measurable concentration
AV	atrioventricular
BLQ	below the limit of quantitation
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
CASI	Computer-Assisted Self-Interview
CBC	complete blood count
CDC	Center for Disease Control
CK	creatine kinase
Clast	the last observed quantifiable plasma concentration of drug
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{min}	minimum plasma concentration
CNS	central nervous system
COBI, /co	cobicistat
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	clinical study report

CYP	cytochrome P450
DBS	dried blood spot
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DRV	darunavir
DSPH	Drug Safety and Public Health. A department at Gilead Sciences that was renamed to Pharmacovigilance and Epidemiology (PVE) effective December 1, 2017.
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EDC	electronic data capture
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
EFV	efavirenz
EVG	elvitegravir
E/C/F/TDF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/ tenofovir disoproxil fumarate (TDF) 300 mg single tablet regimen
E/C/F/TAF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/ tenofovir alafenamide (TAF) 10 mg single tablet regimen
ESDD	Early Study Drug Discontinuation
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
FTC-TP	emtricitabine-triphosphate
F/TAF	emtricitabine/tenofovir alafenamide
F/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practice (Guidelines)
GGT	gamma glutamyl transferase
GSI	Gilead Sciences, Inc.
GS-9137	elvitegravir, EVG, or 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid
GS-9350	cobicistat, COBI, or 2,7,10,12-Tetraazatridecanoic acid, 12-methyl-13-[2-(1-methylethyl)-4-thiazolyl]-9-[2-(4-morpholinyl)ethyl]-8,11-dioxo-3,6-bis(phenylmethyl)-, 5-thiazolylmethyl ester, (3R,6R,9S)-
GS-7340	tenofovir alafenamide, TAF, L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/ phenoxyphosphinyl]-, 1-methylethyl ester
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus antibody
HDPE	high-density polyethylene

HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HMG-CoA	5-hydroxy-3-methylglutaryl-coenzyme A
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor
IMP	Investigational Medicinal Product
IRB	institutional review board
ITT	intent-to-treat (analysis or subset)
IMRS	interactive mobile response system
IWRS	interactive web response system
IXRS	Either IWRS or IMRS
KS	Kaposi's sarcoma
LDH	lactate dehydrogenase
LLN	lower limit of the normal range
LLT	low-level term
MDZ	midazolam
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mmHg	millimeters mercury
MSM	men who have sex with men
NDA	New Drug Application
NNRTI	non-nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
OL	0pen-label
PEP	post-exposure prophylaxis
PBMCs	peripheral blood mononuclear cells
PI	protease inhibitor
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
PRT	proximal renal tubulopathy

PT	preferred term
PVE	Pharmacovigilance and Epidemiology. A department at Gilead Sciences that was renamed from Drug Safety and Public Health (DSPH) effective December 1, 2017.
PY	person years
QD	once daily
QHS	once daily prior to bedtime
RBC	red blood cells
RBP	Retinol-binding Protein
RNA	ribonucleic acid
RPV	rilpivirine
SADR	serious adverse drug reaction
SAE	serious adverse event
SHIV	simian/human immunodeficiency virus
sNDA	Supplemental New Drug Application
SOC	system organ class
SOP	Standard Operating Procedure
STB	Stribild®, EVG/COBI/FTC/TDF (E/C/F/TDF) single tablet regimen
STI	sexually transmitted infection
STR	single tablet regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	estimate of the terminal elimination half-life of the drug in serum/plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TAF	tenofovir alafenamide (GS-7340)
TAF fumarate	tenofovir alafenamide fumarate (GS-7340-03)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate pharmacologically active metabolite (TFVpp)
TGW	transgender women
T_{max}	the time (observed time point) of C_{max}
UACR	urine albumin-to-creatinine ratio
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
UPCR	urine protein-to-creatinine ratio
US	United States
USRDA	United States Recommended Daily Allowances
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cells
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the serum, plasma concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that there were more than 2 million new HIV-1 infections in 2014 despite widespread knowledge of the protective effects of abstinence, monogamy, and condoms in preventing new HIV-1 infections {UNAIDS 2015}. The principal interventions used to prevent HIV transmission have been voluntary testing and counseling and the promotion of condoms. The effectiveness of these interventions has been variable {Coates 2000, Higgins 1991, Wolitski 1997} and the prevalence of HIV-1 infection remains high even in settings with 100% condom promotion policies {Lertpiriyasuwat 2003}. Additionally, new HIV-1 infections in the US have been consistently stable at about 50,000 per year, and 70% of these are in MSM, with or without concurrent injection drug use {Centers for Disease Control (CDC) 2015}; in fact, the proportion of new infections due to male-to-male transmission increased from 2010-2014. Although intense research has been conducted to develop a conventional vaccine against HIV-1 infection, these efforts have failed to produce a viable option. Thus, an important medical need exists for a novel approach to augment HIV-1 prevention services and reduce the spread of HIV-1 infection.

Pre-exposure prophylaxis strategies have been used to prevent transmission of infectious diseases such as malaria and HIV-1. Evidence supporting the efficacy of prophylaxis with antiretroviral therapy (ART) in decreasing HIV-1 seroconversion can be found in experience with post-exposure prophylaxis (PEP) in animal models {Tsai 1995, Van Rompay 2000, Van Rompay 2001} and in other clinical settings such as with occupational exposure with healthcare workers or with maternal-to-child transmission {Gerberding 1993}.

Truvada®, a fixed-dose combination of emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), was first granted marketing approval by the United States (US) Food and Drug Administration (FDA) for use in combination with other agents for the treatment of HIV-1 infection in adults on 02 August 2004. On 16 July 2012, a supplemental New Drug Application (sNDA) 021752/S-030 was approved to expand the use of Truvada in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk. While TDF is an effective drug used broadly (as part of multiple combination regimens) in both the treatment and prevention of HIV-1 infection, nephrotoxicity has been reported with use of TDF and manifests as increased creatinine, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi syndrome). These TDF-associated renal risks necessitate increased renal monitoring, placing burden on the patient and healthcare provider. In addition, early onset bone demineralization in adults has also been reported with use of TDF, specifically reductions in bone mineral density (BMD); the decreases in BMD with TDF are larger than those seen with other NRTIs {Gilead Sciences International Limited 2016, VIREAD® 2016}.

Gilead Sciences has coformulated FTC with tenofovir alafenamide (TAF) into a fixed dose combination for use once daily in combination with other antiretroviral agents for the treatment of HIV-1 in adults and pediatric patients 12 years of age and older. Tenofovir alafenamide is a new prodrug of the N(t)RTI tenofovir (TFV) that is more stable in plasma than TDF. TAF has pharmacokinetic properties that distinguish it from TDF, with clinically important consequences. TAF 25 mg achieves > 4-fold higher intracellular levels of the pharmacologically active phosphorylated metabolite tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMCs) and ~90% lower circulating levels of TFV relative to TDF (300 mg). This marked reduction in circulating TFV is associated with smaller changes in clinical markers of renal function (e.g., proteinuria) and in BMD that are consistent with those seen in subjects receiving non-TDF containing regimens.

Key Phase 3 clinical data from the Genvoya® clinical program demonstrates that F/TAF-containing regimens significantly improve bone safety profile as compared with TDF-based regimens, specifically, significantly less reduction in BMD at both the hip and spine for ART-naive subjects compared to STB, and significant improvements in BMD for subjects who switched from a TDF-based regimen to Genvoya. Additionally the data demonstrates that F/TAF-containing regimens significantly improve renal safety profile as compared with TDF-based regimens, specifically, significantly less change in serum creatinine, proteinuria, and specific renal tubular proteinuria for ART-naive subjects compared with STB; and a significant reduction in serum creatinine levels and significant improvements in renal tubular protein parameters for subjects who switched from a TDF-based regimen to Genvoya.

F/TAF has favorable characteristics that make it suitable for evaluation as chemoprophylaxis, including higher PBMC intracellular concentrations of the pharmacologically active metabolite TFV-DP than TDF-based regimens with potent antiviral effects, a long intracellular half-life of more than 24 hours for TFV-DP, convenient once-daily oral dosing, a favorable tolerability profile, and infrequent selection of drug resistance mutations. Efficacy of F/TAF for chemoprophylaxis has been demonstrated by preventing SHIV infection in a rhesus monkey model (see Section 1.2.2).

Use of F/TAF is less likely to impact bone mineralization in younger adults 18-25 and less likely to impact kidney function in older adults at increased risk of chronic kidney disease. Once commercially available, the use of F/TAF for PrEP in uninfected individuals at high risk may provide an effective prevention regimen with a significantly improved renal and bone safety profile relative to Truvada.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is an oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain. In the development of TAF, three forms of the drug substance have been used

in various studies: GS-7340, synonym for GS-7340 as the free base; GS-7340-02, synonym for TAF monofumarate (1:1); and GS-7340-03 as the hemifumarate (2:1). GS-7340-03, also known as TAF fumarate, is considered comparable based on physical/chemical properties to GS-7340-02 that has been used in previous studies and a number of ongoing studies. GS-7340-03 was also used in the Phase 2 study GS-US-292-0102 and is being used in several ongoing Phase 3 studies (for example: GS-US-292-0104 and GS-US-292-0111). GS-7340-03 and GS-7340-02 exist as the free base, TAF (GS-7340), in blood and biological fluids.

1.2.2. Nonclinical Studies of F/TAF for PrEP

Nonclinical pharmacology studies in rhesus macaques show that orally administered F/TAF, at doses resulting in PBMC exposures that are consistent with those achieved in humans administered a dose of F/TAF 200/25 mg, effectively prevents SHIV infection.

Using a design similar to a previous Centers for Disease Control (CDC) study of F/TDF in rhesus macaques {Garcia-Lerma 2010}, researchers at the CDC demonstrated that oral administration of F/TAF in rhesus macaques prevents infection with a chimeric simian/human immunodeficiency virus (SHIV) (PC-412-2001). The dose of TAF selected for administration in the SHIV viral challenge study was based on an initial pharmacokinetic study in macaques wherein a TAF dose of 1.5 mg/kg was shown to result in intracellular concentrations of the active moiety TFV-DP in PBMCs consistent with those seen with use of a TAF 25 mg dose in humans (see PK section below). FTC was dosed at 20 mg/kg based on a similar rationale, and consistent with the previous study with F/TAF in macaques. In the SHIV viral challenge study, 12 healthy rhesus macaques were administered weekly inoculations of intrarectal SHIV. Twenty-four hours before each rectal inoculation and 2 hours after each rectal inoculation, one group of 6 animals were administered 20 mg/kg FTC and 1.5 mg/kg TAF by oral gavage and one group of 6 animals were administered placebo (saline control) by oral gavage. SHIV challenges and paired gavages were administered once a week for up to 19 weeks (schematic of the study design is provided in Figure 1-1). All 6/6 macaques given placebo (saline control) became infected with SHIV, while 0/6 macaques given F/TAF became infected with SHIV (results shown in Figure 1-2).

Figure 1-1. Design of Study PC-412-2001 of F/TAF for PrEP in Rhesus Macaques

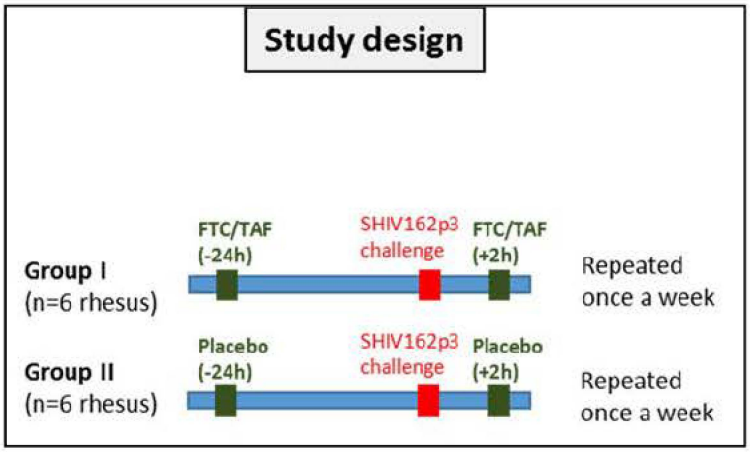
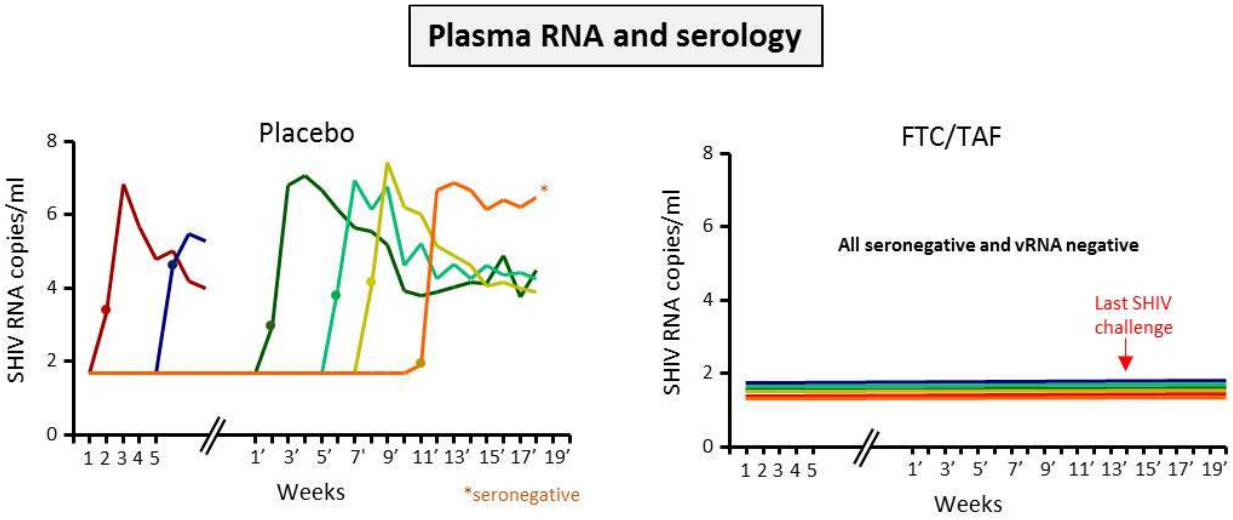


Figure 1-2. Plasma RNA and Serology Results from Study PC-412-2001 of F/TAF for PrEP in Rhesus Macaques



Note: Each colored line represents an individual rhesus monkey. The Weeks 1-5 represent viral challenges with the initial viral stock. Weeks 1'-19' represent viral challenges with a second viral stock with higher infectivity.

The dose of TAF used in Study PC-412-2001 was chosen to target the PBMC exposure range observed in humans following administration of TAF 25 mg. While the definitive correlate of protection against mucosal viral exposure is not established, intracellular levels of TFV-DP have been consistently associated with both virologic suppression and with prophylaxis across a variety of human and animal studies {Abdool Karim 2010, Anderson 2012, Baeten 2012, Castillo-Mancilla 2013, Garcia-Lerma 2008, Grant 2010, Van Rompay 2012, Van Rompay 2001}.

The results of Study PC-412-2001 in rhesus macaques are consistent with the previously published CDC study of FTC and TDF conducted in the same non-human primate model {Garcia-Lerma 2010}. In the prior SHIV viral challenge study, rhesus macaques were inoculated with SHIV once a week for 14 weeks via intrarectal administration. Various dosing regimens using orally administered 20 mg/kg FTC and 22 mg/kg TDF (given 1, 3, or 7 days before exposure followed by a second dose 2 hours after exposure) were evaluated. In that study, 5 of 6 animals given oral F/TDF at 24 hours prior to SHIV inoculation and 2 hours after SHIV inoculation at doses equivalent to those administered to humans for treatment remained seronegative through 14 inoculation challenges of rectally administered SHIV. Protection against SHIV in rhesus macaques subject to rectal challenge has also been observed following daily subcutaneous administration of 20 mg/kg FTC and 22 mg/kg TFV, suggesting that local concentrations possible in the gastrointestinal tract following oral administration are not required for protection and that systemic loading of HIV-target cells (i.e. PBMCs) drives efficacy {Garcia-Lerma 2008}.

1.2.3. Preclinical Pharmacology and Toxicology

1.2.3.1. Primary Pharmacodynamics

TAF is metabolized to TFV, a nucleotide analog (i.e., a nucleoside monophosphate analog) which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV diphosphate (TFV-DP). The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) {Tsai 1995} and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2.

The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was also studied in different human blood lymphocyte subpopulations, CD4+ and CD8+ T-cells, NK cells, B-cells and macrophages/monocytes. TAF is metabolized inside host cells to the active metabolite TFV-DP. Concentration of the active metabolite TFV-DP was substantial in all cell populations.

1.2.3.2. Safety Pharmacology

TAF monofumarate (GS-7430-02) has been evaluated to determine potential effects on the central nervous system (R990188), renal system (R990186), cardiovascular (D2000006) and gastrointestinal systems (R990187). Single doses did not induce pharmacologic effects on the central nervous system of the rat (1000 mg/kg), the renal system of the rat (1000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF monofumarate (at 1000 mg/kg reduced distal transit and increased stomach weights starting 2 hours postdosing with reversibility beginning by 6 hours after dosing. The NOEL for gastrointestinal motility was 100 mg/kg. The IC_{50} for the inhibitory effect of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 µM.

1.2.4. Nonclinical Pharmacokinetics

All nonclinical pharmacokinetic experiments in this section were performed using TAF monofumarate (GS-7340-02), and all study data described in this section reflect the dosage of the monofumarate. For reference, 100 mg of TAF monofumarate is equivalent to 80 mg of the GS-7340 free base (TAF).

Plasma pharmacokinetics of the intact prodrug, TAF, following oral administration of GS-7340-02 in dogs and monkeys demonstrated rapid absorption with peak plasma concentrations between 0.25 and 0.5 hours.

Peak TFV plasma concentrations occurred following TAF absorption, with TFV T_{max} values between 0.25 to 1.7 hours in rats, dogs, and monkeys. TFV plasma concentrations declined with a terminal half-life of 11.2 to 16.4 hours in rats (fasted), > 24 hours in dogs (fasted) and 8.1 to 12.5 hours in rhesus monkeys.

The tissue distribution and recovery of [^{14}C] radiolabeled GS-7340-02 was examined in beagle dogs. Radioactivity was detected in all tissues except brain, with the majority present in the contents of the gastrointestinal tract, liver, kidney, and large intestine. Tissue concentrations were the highest in kidney, PBMCs, liver, large intestine, and bile. Significant concentrations of TFV-related radioactive material were observed in lymph nodes suggesting that TAF may be selectively cleaved to tenofovir in the cells of the lymphoreticular system.

The primary route of elimination of tenofovir is renal excretion of unchanged drug based on IV studies of tenofovir. Following oral administration of GS-7340-02, approximately 15% of a radiolabeled dose is recovered in dog urine in 24 hrs. Tenofovir was the major species present in the urine (90%), with about 3.4% of TAF also present. Biliary excretion of tenofovir in dogs and fecal elimination of tenofovir in rats and dogs are negligible.

Tenofovir was the only species found in the intestinal contents and feces. In human systems, TAF is metabolized by hydrolytic cleavage and, to a lesser extent, by CYP3A4 catalyzed oxidation (AD-120-2004). As a result of the limited metabolism of TAF by CYP3A4 inhibition or induction of this enzyme should have little consequence on TAF exposure in vivo. TAF has limited potential to alter CYP enzyme activity through inhibition and does not inhibit UGT1A1 function. In addition, TAF is not an activator of either the aryl hydrocarbon receptor (AhR) or human pregnane-X-receptor (PXR). These features combined with the relatively low plasma exposures of TAF in humans suggest that the potential of TAF to cause or be affected by clinically relevant drug-drug interactions is very low.

1.2.5. Nonclinical Toxicology

TAF monofumarate (GS-7340-02) was evaluated in mice, rats, dogs, and monkeys for treatment periods up to 9-months and was negative in genetic toxicology studies.

In chronic studies in rats, bone (atrophy of metaphyseal cancellous bone) and kidneys (karyomegaly) were the primary target organs after 26 weeks of treatment. GS-7340-02 also appeared to increase biochemical markers of bone turnover and decrease serum 1,25-dihydroxy- and 25-hydroxyvitamin D3 at doses of 25 mg/kg/day and above. In chronic studies in dogs after 9 months of treatment with GS-7340-02, the primary target organs were kidney and bone. This chronic toxicity study of TAF in beagle dogs given 2mg/kg/day, 6 mg/kg/day or 12-18 mg/kg/day for 9 months found non-specific mononuclear cell infiltrates seen on histopathology in the lungs, spleen and posterior uvea (eye) of animals in the 12-18 mg/kg group. This group of animals experienced generalized debility at the 18 mg/kg/day dose, so the dose was decreased after Week 6. The histopathologic changes were felt to be due to the overall condition of the animals and not specific TAF-related toxicity. There were no findings in the eyes of dogs treated with lower doses (2 mg/kg and 6 mg/kg), and it was concluded that the NOAEL in beagle dogs was 2 mg/kg/day.

TAF monofumarate had no discernible electrocardiograph effect at the low dose of 2 mg/kg/day and slightly prolong PR intervals at 6 and 12-18 mg/kg/day. Additionally, at Week 39, TAF monofumarate appeared to reversibly reduce heart rate with an associated mild QT prolongation. At Week 39, decreases in serum T3 were noted for animals receiving

18/12 mg/kg/day but was reversible at the 3-month recovery period. Minor hematological and biochemistry parameters changes were observed but remained within normal historical ranges with the following exceptions: AST (~100% increase) and total bilirubin (~40% increase). There were no clear treatment-related effects observed in monkeys following 28 days of treatment including no changes in mitochondrial function.

The data from the 6-month rat study determined a NOAEL of 25 mg/kg/day (tenofovir AUC = 3758 ng•h/mL); the 9-month dog study defined a NOAEL of 2 mg/kg/day (tenofovir AUC = 1180 ng•h/mL), and the 28-day nonhuman primate study defined a NOAEL of 30 mg/kg/day (tenofovir AUC = 5870 ng•h/mL). In conjunction with the nonclinical data with TDF and the clinical experience with TDF and TAF, these toxicology studies support studies in humans of doses up to 150 mg/day (120 mg free base, the highest anticipated human dose) for chronic treatment.

At the time of the rodent toxicity studies, the bioassay could not detect plasma TAF, possibly due to instability in the matrix.

Because of the lack of exposure to the prodrug in mice and rats and achievable tenofovir exposures less than previously tested in chronic and carcinogenicity studies with TDF, carcinogenicity studies in mice and rats with TAF are not required per agreement with the FDA.

Also, TAF does not need to be evaluated in perinatal-postnatal reproductive toxicology studies per agreement with the FDA. Reproductive tissues were examined in repeat-dose toxicology studies in the rat, dog, and monkey. There were no clearly treatment-related histologic alterations or changes in organ weights in the rat and the dog following chronic daily dosing, or in the monkey.

The TAF fumarate (GS-7340-03) oral rat fertility study is ongoing (Report No. TX-120-2012, report in progress).

1.2.6. Clinical Trials of Single Agent Tenofovir Alafenamide (TAF, GS-7340) or Fixed Dose Combination Emtricitabine/Tenofovir Alafenamide (F/TAF)

Clinical trials entailing the use of tenofovir alafenamide include:

- **GS-US-120-1101**, a Phase 1/2 study of the pharmacokinetics and antiviral activity of GS-7340 (50 mg and 150 mg) in HIV-infected subjects (completed)
- **GS-US-120-0104**, a Phase 1b study of the pharmacokinetics and antiviral activity of GS-7340 (8 mg, 25 mg, 40 mg) in HIV infected subjects (completed)
- **GS-US-120-0107**, a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-7340 on the QT/QTc interval in healthy subjects (completed)
- **GS-US-120-0108**, a Phase 1, open-label, parallel-design study to evaluate the pharmacokinetics of GS-7340 in subjects with severe renal impairment (completed)
- **GS-US-120-0109**, a Phase 1 study to evaluate the pharmacokinetics, metabolism and excretion of GS-7340 (completed)

- **GS-US-120-0114**, a Phase 1, open-label, parallel-group, single dose study to evaluate the pharmacokinetics of tenofovir alafenamide in subjects with normal and impaired hepatic function (ongoing)

- **GS-US-120-0117**, a Phase 1 single-dose study evaluating the pharmacokinetic drug interaction potential between rilpivirine and tenofovir alafenamide (ongoing)

- **GS-US-120-0118**, a Pharmacokinetic study evaluating the drug interaction potential of tenofovir alfenamide with a boosted protease inhibitor or unboosted integrase inhibitor in healthy subjects

- **GS-US-311-0101**, a Phase 1 healthy volunteer study evaluating the drug interaction potential between once-daily FTC/GS-7340 fixed-dose combination and efavirenz (EFV) or COBI-boosted darunavir (DRV) (completed)

- **GS-US-311-1088**, a Phase 1, Relative Bioavailability Study of Emtricitabine/Tenofovir Alafenamide Fixed Dose Combination Tablet to evaluate the formulation performance of emtricitabine (FTC) and tenofovir alafenamide (TAF) fixed dose combination tablets relative to co-administration of individual agents (currently being planned).

The first proof-of concept study, GS-US-120-1101, as well as GS-US-120-0104 and GS-US-292-0101 were performed using TAF monofumarate (GS-7340-02). All subsequent studies were performed using TAF fumarate (GS-7340-03), with the exception of GS-US-311-0101 Cohort 4, which used the monofumarate (GS-7340-02) for the GS-7340 single agent 8 mg tablet.

GS-US-120-1101 was a Phase 1/2 randomized double-blind, active-controlled, dose escalation study of the safety, tolerance, pharmacokinetics, and antiviral activity of TAF in antiretroviral-naïve patients who are chronically infected with HIV-1. The subjects were randomized to receive 14 days of monotherapy, fasting, with TAF monofumarate 50 mg once daily, 150 mg once daily, or tenofovir disoproxil fumarate 300 mg once daily (n=10 per group). TAF was rapidly absorbed into the systemic circulation, and following attainment of C_{max}, was eliminated rapidly with a short plasma half-life (20-40 minutes). Compared with TDF, TAF monofumarate 50 mg provided a ~16-fold lower tenofovir C_{max} (207 ng/mL vs 13 ng/mL), about two-fold longer elimination half-life (26 hours vs 48 hours) and lower overall systemic tenofovir exposure (AUC_{inf}: 1814 ng•h/mL vs 383 ng•h/ml). TAF monofumarate 150 mg provided lower C_{max} (42 ng/mL), but comparable AUC_{inf}: (1740 ng•h/mL) as TDF. In PBMCs, tenofovir was detectable earlier, more frequently, and in higher concentrations following dosing of TAF monofumarate. The intracellular delivery of tenofovir is approximately 30-fold greater for TAF monofumarate versus TDF. The decrease from Baseline to Day 14 in plasma HIV-RNA levels was greater for groups treated with TAF monofumarate 50 mg ($p = 0.0257$) or 150 mg ($p = 0.0010$) than the group that received TDF 300 mg. The median changes from baseline in plasma HIV-1 RNA after 14 days of monotherapy were -0.96 $\log_{10}$ copies/mL for TDF 300 mg, -1.65 $\log_{10}$ copies/mL for TAF monofumarate 50 mg, and -1.68 for TAF monofumarate 150 mg.

A second proof-of-concept study, GS-US-120-0104, evaluated monotherapy, with three lower doses of TAF or TDF 300 mg, or placebo, administered in a fasted state for 10 days. Potent antiviral activity was achieved in treatment-naïve HIV-1 infected patients, with mean (± SD) change from baseline in HIV-1 RNA of −0.98 ± 0.46, −1.50 ± 0.41, −1.74 ± 0.19, and −0.81 ± 0.58 log10 copies/ml at 8 mg, 25 mg, 40 mg dose of TAF, and TDF 300 mg, respectively. Mean viral load declines for both the 25 mg and 40 mg doses were statistically greater than the 8 mg dose. TAF exposure (AUC) was best associated with antiviral activity despite its short plasma half-life (~30 min). TFV AUC were 97%, 87%, and 80% lower at 8 mg, 25 mg, and 40 mg TAF compared to TDF administration. When compared to 40 mg and historical 120 mg data, 25 mg TAF provides near maximal activity (predicted to be ~ −1.7 to1.8 log10 c/mL). From this PK-PD analysis, a target dose of 20-25 mg TAF monotherapy is expected to provide near maximal activity and ~90% reduction in circulating TFV.

Study GS-US-120-0107 is a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of TAF on the QT/QTc interval in healthy subjects. This was a negative thorough QTc study. No effect of TAF was observed on the QTcF interval (ie, no QTc interval prolongation > 10 msec at any time point post-dose and assay sensitivity was confirmed via the positive control [moxifloxacin]). As such, these findings satisfy the guidelines set forth in the International Conference on Harmonization (ICH) E14 guidance and support the conclusion that there is no significant effect of TAF on the QT/QTc interval.

Study GS-US-120-0108 was a Phase 1, open-label (OL), parallel-design study to evaluate the PK of TAF in subjects with severe renal impairment. TAF was well tolerated in the study. Patients with severe renal impairment had < 2-fold higher TAF and 5-6 fold higher TFV systemic exposures as assessed by AUC relative to subjects with normal renal function. TFV exposures in subjects with severe renal impairment are comparable to those with normal renal function receiving 300 mg TDF. Given the extensive safety data available for TDF at a dose of 300 mg, TFV exposures in severely renally impaired subjects similar to those associated with TDF 300 mg are deemed appropriate for further study of TAF in HIV-infected patients without TAF dose modification.

1.3. Emtricitabine (FTC, Emtriva®)

Further information regarding Emtriva® is available in the prescribing information, an overview is provided below.

1.3.1. General Information

Emtricitabine (5-fluoro-1-[(2R, 5S)-2-(hydroxymethyl)-[1, 3]-oxathiolan-5-yl] cytosine, FTC) is a NRTI that has demonstrated potent and selective inhibition of the HIV. In HIV-infected adults, FTC is administered as a 200 mg QD dose concurrently with other ARV drugs. The 200 mg FTC capsule formulation was approved by the US Food and Drug Administration (FDA) for marketing on 2 July 2003 and is available under the name Emtriva. In the European Union (EU), marketing authorization was granted for both the 200 mg Emtriva capsule formulation and a 10 mg/mL Emtriva oral Solution formulation on 24 October 2003, with indications for the

treatment of HIV infection concurrently with other antiretroviral drugs in both adult and pediatric patients. In pediatric patients, the recommended dose of Emtriva is 6 mg/kg QD, up to a maximum of 200 mg QD when administered using the capsule formulation (for children weighing > 33 kg) or up to a maximum of 240 mg when administered using the oral solution formulation.

1.4. Fixed-Dose Combination of Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF)

Further information is available in the Prescribing Information for Truvada® (emtricitabine/tenofovir disoproxil fumarate).

1.5. Rationale for This Study

Based on available data, the use of F/TAF for PrEP would provide a new option for persons with high sexual risk of HIV-1 acquisition. Based on data with F/TAF based regimens used for treatment of chronic HIV-1 infection, the improved safety profile of F/TAF (relative to F/TDF) reduces the risk of a negative impact on bone mineralization in younger adults (18-25 years of age) who are still in a bone growth phase, and also reduces the risk of a negative impact on renal function in older adults with risk factors for chronic kidney disease. Use of F/TAF once daily for PrEP is expected to be similarly efficacious to Truvada but also have an improved safety profile.

Nonclinical pharmacology studies in rhesus macaques show that orally administered F/TAF, at doses resulting in PBMC exposures that are consistent with those achieved in humans administered a dose of F/TAF 200/25 mg, effectively prevents SHIV infection.

Oral administration of TAF results in rapid accumulation of TFV-DP in the intracellular PBMC compartment with levels that are at least 4 fold higher than with use of TDF. When used as monotherapy for 10 days (Study GS-US-120-0104), TAF 25mg has increased antiviral potency relative to TDF 300 mg. Treatment of chronic HIV-1 infection with TAF-based regimens have similar or higher rates of undetectable viral load at 48 and 96 weeks when administered as Genvoya compared to Stribild® in treatment-naïve patients, and when administered as F/TAF + a third agent in virologically suppressed patients who switch from a Truvada-based regimen to F/TAF (Study GS-US-311-1089). Refer to the Genvoya Prescribing Information for more details.

There is considerable data demonstrating that F/TAF (administered as either Genvoya or as F/TAF + a third agent) has statistically significant improvement in both renal and bone safety profiles in both treatment-naïve patients and in virologically suppressed patients who switch from a TDF based regimen (Refer to the Genvoya Prescribing Information for more details). These improvements in measures of renal and bone safety, most notably no reported cases of proximal renal tubulopathy (including Fanconi Syndrome), are most likely due to the 90% reduction in plasma TFV levels observed in subjects receiving TAF-based regimens. The use of F/TAF for PrEP to reduce the risk of sexually acquired HIV-1 in uninfected individuals at high risk may provide an effective prevention regimen with a significantly

improved renal and bone safety profile relative to Truvada. This is of particular importance for HIV-1 negative persons who are otherwise likely to be healthy, in whom the acceptability of medication related risks relative to benefit must be weighed carefully.

The present study will be conducted in MSM and TGW who are at least 18 years of age, a population consistently at highest risk of HIV-1 acquisition through sexual behavior.

1.6. Rationale for Dose

The 200 mg dose represents the dose of FTC in the fixed-dose combination Truvada, which is approved for a PrEP indication in the United States.

Based upon results of the Phase 1 Study GS-US-120-0104, in which increasing doses of TAF (8 mg, 25 mg, and 40 mg) were administered to HIV-1-infected subjects in 10 days of monotherapy, the range of plasma and PBMC exposure achieved with TAF 25 mg was chosen as the reference exposure. In this study, TAF 25 mg resulted in near-maximal antiviral activity with significantly increased TFV-DP levels in PBMCs and significantly decreased plasma TFV exposure relative to TDF.

The recommended dose of TAF is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered as Genvoya, for which an extensive efficacy and safety database exists. The recommended TAF dose (10 or 25 mg) is based on whether or not the co-administered third agent requires a pharmacokinetic enhancer. As F/TAF for PrEP will be administered in the absence of a third antiretroviral agent, the 25 mg dose of TAF (with FTC 200 mg) has been selected for evaluation in the proposed Phase 3 study.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To assess the rates of HIV-1 infection in men (MSM) and transgender women (TGW) who have sex with men who are administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization

The secondary objectives of this study are:

- To compare bone safety between the treatments as determined by dual energy x-ray absorptiometry (DXA) tests of hip and spine bone mineral density (BMD) in a subset of participants at Week 48 and Week 96 in the blinded phase
- To compare renal safety between the treatments as determined by urine retinol-binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, urine protein to creatinine ratio (UPCR), and serum creatinine at Week 48 and Week 96 in the blinded phase
- To assess the rates of HIV-1 infection in men (MSM) and transgender women (TGW) who have sex with men who are administered daily F/TAF or F/TDF when all subjects have 96 weeks of follow-up after randomization
- To compare the general safety between the treatments

Exploratory objectives of this study include:

3. STUDY DESIGN

3.1. Endpoints

3.1.1. Primary Endpoint

The primary endpoint will be the incidence of HIV-1 infection per 100 PY when all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization. HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated subjects, or

2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or

3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

Please refer to Appendix 6 for more details.

3.1.2. Secondary Endpoints

The key (α-controlled) secondary endpoints in the blinded phase are (in the following order):

- The percent change from baseline in hip BMD at Week 48 in a subset of subjects
- The percent change from baseline in spine BMD at Week 48 in a subset of subjects
- Assessment of renal biomarkers at Week 48
  - — percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - — percent change from baseline in urine RBP to creatinine ratio
  - — distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 48

Other secondary endpoints include:

- The incidence of HIV-1 infection (as defined by Appendix 6) per 100 PY when all subjects have 96 weeks of follow-up after randomization
- The percent change from baseline in hip and spine BMD at Week 96 in the blinded phase in a subset of subjects

- Assessment of renal biomarkers at Week 96 in the blinded phase
  - percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - percent change from baseline in urine RBP to creatinine ratio
  - distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 96 in the blinded phase
- The incidence of treatment-emergent adverse events and laboratory toxicities

3.1.3. Other Endpoints of Interest

- The intracellular TFV-DP and FTC-TP trough concentrations (C_{trough}) in PBMCs
- The adherence rate using TFV-DP levels in DBS along with plasma FTC and/or TFV levels
- The incidence of HIV-1 infection per 100 PY at OL Week 48 for those who randomize to the F/TAF arm at baseline
- From the OL phase baseline to OL Week 48, percentage change in hip and spine BMD (in a subset of subjects), assessment of renal biomarkers (percent change in urine beta-2-microglobulin to creatinine ratio and urine RBP to creatinine ratio, distribution of UP and UPCR categories), and change from baseline in serum creatinine for those who switch to F/TAF from F/TDF in the OL phase
- The type and frequency of sexual practices that are associated with increased risk of HIV-1 infection

3.2. Study Design

This protocol describes a randomized, double-blind comparison of the safety and efficacy of F/TAF versus F/TDF administered once daily (QD) for at least 96 weeks in HIV-1 negative adult MSM or TGW (male at birth) who have sex with men and are at risk of HIV-1 infection.

All subjects must meet all eligibility criteria in order to receive treatment in the study. Once randomized to receive treatment in the study, all subjects must return to the study center for required visits at Weeks 4, 12, and every 12 weeks thereafter.

All subjects will remain blinded to study treatment for at least 96 weeks. The primary endpoint data will be collected and analyzed when all subjects have a minimum follow-up of 48 weeks and 50% of the subjects have 96 weeks of follow-up after randomization.

Once all subjects have at least 96 weeks of follow-up after randomization and upon notification by Gilead, all subjects will return to the study center for an End of Blinded Treatment Phase visit (may coincide with their next scheduled visit).

Subjects who are still on blinded study drug at the End of Blinded Treatment Phase visit will be offered entry into the 48 week OL phase of the study. Subjects who continue participation in the OL phase will be administered F/TAF QD and will return to the study center for visits at OL Weeks 12, 24, 36, and 48.

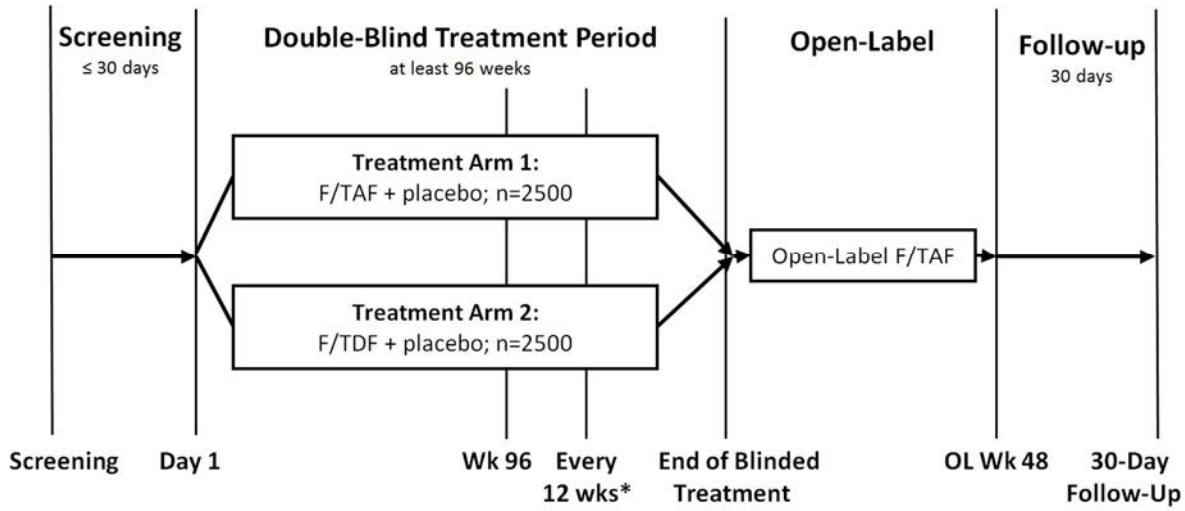
Subjects who have discontinued study drug prior to the End of Blinded Treatment Phase visit due to HIV infection will be eligible to continue participation in the OL phase, but will not be administered F/TAF QD. Subjects who have discontinued study drug for any other reason prior to the End of Blinded Treatment Phase visit will not be eligible to participate in the OL Phase.

After subjects in the OL phase of the study have completed 48 weeks of treatment, the study will be considered clinically complete and subjects should be transitioned to commercially available drug supplies. However, subjects in geographic regions where F/TAF is not commercially available for use as PrEP at the completion of the OL phase will be able to continue on F/TAF until F/TAF becomes commercially available, or until Gilead Sciences terminates clinical development of F/TAF for PrEP. These subjects will continue OL study visits every 12 weeks. Subjects in Denmark and the United Kingdom are ineligible for this continued treatment option and must discontinue study drug at the OL Week 48 visit and return 30 days later for a 30 Day Follow-Up visit. Subjects who are HIV infected will discontinue from the study at OL Week 48.

During the blinded treatment phase, subjects may choose to continue to participate in the study without taking study drug (“on-study, off-study drug”). Subjects who permanently discontinue study drug and continue to attend normal study visits (at minimum one visit at least 30 days after last dose) are not required to complete the follow-up visit. Any subject who has an Early Study Drug Discontinuation (ESDD) visit and who will not continue participating in the study, or any subject who will not continue participation in the OL phase of the study, must complete the 30 Day Follow-Up visit 30 days after the last dose of study drug.

DXA scans will be performed during regular intervals throughout the study (blinded and OL phase) in a subset of approximately 400 subjects at a subset of sites (excluding Germany).

Figure 3-1. Study Schema



* Subjects will continue blinded treatment until the last subject has reached Week 96, and upon notification by Gilead, all subjects will return to the study center for the End of Blinded Treatment Phase visits.

3.3. Study Treatments

Blinded Phase:

Subjects who provide written consent and meet all eligibility criteria will be randomized in a 1:1 ratio to one of the following two treatment arms:

- **Treatment Arm 1:** F/TAF (200 mg/25 mg) + placebo-to-match F/TDF (n =2500)
- **Treatment Arm 2:** F/TDF (200 mg/300 mg) + placebo-to-match F/TAF (n = 2500)

Open Label Phase:

During the open-label phase, all subjects will be administered open-label F/TAF (200 mg/25 mg).

3.4. Biomarker Testing

3.4.1. Biomarker Samples to Address the Study Objectives

Urine samples as outlined in Section 6.13 will be collected in this study and may be used to evaluate the association of renal biomarkers with study drug response. The specific analyses may not be limited to the renal biomarkers and assays. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. Biological markers (for example serum or plasma analytes [protein markers]) are indicators which may help in understanding HIV-1 infection and related diseases.

Blood samples will be collected in this study for subjects who become HIV infected on the GS-US-412-2055 study as per the timepoints listed in Appendix 2 and will be used to evaluate the association of exploratory inflammation and immune biomarkers with antiretroviral treatment, including efficacy and/or adverse events to explore the biology of early HIV-1 infection and related diseases. The specific analyses may not be limited to the inflammatory/immune biomarkers and assays. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. Biological markers (for example serum or plasma analytes [protein markers]) are indicators which may help in understanding HIV-1 infection and related diseases.

These samples may be stored by Gilead Sciences up to a period of 15 years.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

5000 subjects who meet all of the Inclusion and none of the Exclusion criteria will be enrolled.

4.2. Inclusion Criteria

Subjects must be at high risk of sexual acquisition of HIV and meet *all* of the following inclusion criteria to be eligible for participation in this study.

1) HIV-1 negative status

2) MSM or TGW (male at birth) who have at least one of the following:

   a) condomless anal intercourse with at least two unique male partners in the past 12 weeks (partners must be either HIV-infected or of unknown HIV status)

   b) documented history of syphilis in the past 24 weeks

   c) documented history of rectal gonorrhea or chlamydia in the past 24 weeks

3) Age ≥ 18 years

4) Estimated GFR ≥ 60 mL/min according to the Cockcroft-Gault formula for creatinine clearance {Cockcroft 1976}:

$$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} = CL_{cr}\ (\text{mL/min})$$

5) Adequate liver and hematologic function:

   - AST and ALT ≤ 2.5 × upper limit of normal (ULN); and total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin

   - Absolute neutrophil count ≥ 1000/mm^3; platelets ≥ 75,000/mm^3; hemoglobin ≥ 10 g/dL

6) Willing and able to comply with study procedures

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Known hypersensitivity to the IMP, the metabolites, or formulation excipient.

2) Have a suspected or known active, serious infection(s)

3) Acute viral hepatitis A, B or C or evidence of chronic hepatitis B infection. Subjects found to be susceptible to HBV infection should be referred for HBV vaccination. Subjects found to be positive for HCV at screening must not have active infection or must have completed treatment and achieved a sustained virologic response.

4) Need for continued use of any contraindicated concomitant medications

5) Have an implanted defibrillator or pacemaker

6) Have a history of osteoporosis or bone fragility fractures

7) Current alcohol or substance abuse judged by the Investigator to be problematic such that it potentially interferes with subject study compliance

8) Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable.

9) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with dosing requirements

10) Have received investigational agents for the treatment or prevention of HIV-1 infection in the 30 days prior to screening

11) Participation in any other clinical trial (including observational trials) without prior approval from the sponsor is prohibited while participating in this trial

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

This is a randomized, double-blind study.

It is the responsibility of the Investigator to ensure that the subject is eligible for the study prior to randomization.

Randomization cannot occur until subject eligibility has been confirmed. Once eligibility has been confirmed, each subject will be assigned a unique subject number using IXRS: either Interactive Web Response System (IWRS) or Interactive Mobile Response System (IMRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject.

Subjects will be randomized in a 1:1 ratio to Treatment Arm 1 or Treatment Arm 2.

IXRS will assign study drug bottle numbers at each study visit until the subject's last study visit. Study drug will be dispensed to the subject in a blinded fashion from Day 1 through the End of Blinded Treatment Phase visit. All Day 1 visit tests and procedures must be completed prior to the administration of the first dose of the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit. Study drug will be dispensed to the subject in an open-label fashion from the End of Blinded Treatment Phase visit through the final study visit.

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the IXRS system for that subject. Gilead strongly recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Sciences Pharmacovigilance and Epidemiology (PVE) may independently unblind cases for expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs).

5.2. Description and Handling

5.2.1. Formulation

5.2.1.1. Emtricitabine/Tenofovir Alafenamide (F/TAF) 200 mg/25 mg and Matching Placebo

Emtricitabine 200 mg/tenofovir alafenamide 25 mg tablets are blue, rectangular-shaped, film-coated tablets, debossed with "GSI" on one side of the tablet and with "225" on the other side of the tablet. Each tablet core contains 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. In addition to the active ingredients, the F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film-coated with FD&C blue #2/ indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Placebo-to-match F/TAF tablets are identical in appearance to the active tablets and are blue, rectangular-shaped, film-coated tablets. Placebo tablets contain croscarmellose sodium, magnesium stearate, lactose and microcrystalline cellulose. The tablet cores are film-coated with Blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.1.2. Emtricitabine/Tenofovir Disoproxil Fumarate (F/TDF) Tablets and Matching Placebo

Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg tablets are blue, capsule-shaped, film coated tablets debossed with "GILEAD" on one side and are plain-faced on the other side of the tablet. Each tablet core contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. In addition to active ingredients, the F/TDF tablets contain microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, lactose monohydrate and magnesium stearate. The tablet cores are film coated with FD&C blue #2/ indigo carmine aluminum lake, lactose monohydrate, hypromellose, titanium dioxide and triacetin.

Placebo-to-match F/TDF tablets are identical in appearance to the active tablets and are blue, capsule-shaped, film-coated tablets. Placebo tablets contain denatonium benzoate, lactose monohydrate, pregelatinized starch, croscarmellose sodium and magnesium stearate. The tablet cores are film-coated to mask taste. The film coating consists of FD&C blue #2/indigo carmine aluminum lake, lactose monohydrate, hypromellose, titanium dioxide, and triacetin.

5.2.2. Packaging and Labeling

F/TAF tablets and placebo-to-match F/TAF tablets are packaged in a white high density polyethylene (HDPE) bottle. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

F/TDF tablets and placebo-to-match F/TDF tablets are packaged in a white high density polyethylene (HDPE) bottle. Each bottle contains 30 tablets and silica gel desiccant. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

Study drug(s) bottles to be distributed to centers in the US and EU shall be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice − Annex 13 (Investigational Medicinal Products), and/or other local regulations as applicable.

5.2.3. Storage and Handling

F/TAF and the placebo-to-match F/TAF tablets should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

F/TDF and the placebo-to-match F/TDF tablets should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration

F/TAF, placebo-to-match F/TAF, F/TDF, and placebo-to-match F/TDF tablets will be provided by Gilead Sciences. Study drug will be dispensed to subjects at the Day 1 visit. Subjects will be instructed to take their first dose of study medication following completion of the study procedures at the Day 1 visit. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit and after the investigator has confirmed eligibility with the subject.

Subjects will be instructed to bring all study medication in the original container at each clinic visit for drug accountability.

5.4. Prior and Concomitant Medications

Medications and use of herbal/natural supplements listed in the following table are excluded or should be used with caution while subjects are taking study drug on the study due to potential drug-drug interactions with F/TAF.

Table 5-1. Prior and Concomitant Medications

Medication Class	Medications to be Used with Caution	Prohibited Medications
Antiarrhythmics	amiodarone, quinidine: May increase concentration of TAF and/or TFV	
Anticonvulsants		carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	clarithromycin: may increase concentration of TAF and/or TFV	rifapentine, rifabutin, rifampin
Antifungals	itraconazole, ketoconazole, voriconazole: may increase concentration of TAF and/or TFV	
Calcium channel blockers	diltiazem, felodipine, verapamil: may increase concentration of TAF and/or TFV	
Digoxin	Concomitant use may result in an increased or decreased digoxin concentration; use with caution and with appropriate monitoring of serum digoxin concentrations.	
Herbal/Natural Supplements		St. John's Wort, echinacea, milk thistle (e.g. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Hepatitis C therapies	Ledipasvir/sofosbuvir: has been shown to increase tenofovir exposure	boceprevir, telaprevir
Nephrotoxic medications	high dose or multiple NSAIDS	systemic chemotherapeutic agents, aminoglycoside antibiotics, amphotericin B, cidofovir, cisplatin, foscarnet, IV pentamidine, or, other agents with significant nephrotoxic potential
Systemic glucocorticoids		dexamethasone (more than 1 dose), or chronic use of other systemic glucocorticoids
Other		probenecid

Should subjects have a need to initiate treatment with any prohibited concomitant medication, the Gilead Medical Monitor must be consulted and approval granted prior to initiation of the new medication. In instances where a prohibited medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the prohibited medication.

5.5. Dispensing and Accountability of Investigational Medicinal Product

The Investigator is responsible for ensuring adequate accountability of all used and unused Investigational Medical Product (IMP) or study drug. The Investigator [or designee (e.g., study center pharmacist)] will acknowledge receipt of the study drugs from Gilead Sciences (or designee) after reviewing the shipment's content and condition. The Investigator (or designee) will be responsible for maintaining an accurate inventory (on IMP accountability records) of the dates and quantities of all study drugs received, dispensed, and returned. The requirements of all applicable Federal and State drug dispensing laws will apply to all doses of study drugs dispensed by the Investigator (or designee).

The IMP inventory and dispensing logs must be available for inspection by the study monitor. Study medication supplies, including partially used or empty bottles, must be accounted for by the study monitor prior to destruction or return.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible for study prior to enrollment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

The following assessments will be performed at the Screening visit:

- Written informed consent completed prior to any other assessments
- Medical history including information about alcohol use in the past year and self-reported sexual risk events and medications used by the participant in the 30 days prior to the Screening visit
- Complete physical examination, vital signs measurements (blood pressure, pulse, respiration rate, and temperature), height and weight
- Sexually transmitted infection (STI) testing. Subjects who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the subject at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- 4^{th} generation rapid HIV-1 Ab/Ag or 3^{rd} generation rapid HIV-1 Ab test. If test is positive, a retest will be completed. If the retest is positive, the subject is a screen failure.
  - Any subject with a positive repeat HIV-1 rapid test will receive counseling and be referred for appropriate care

- Urine sample for dipstick urinalysis (per local lab)
- Urine sample for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine)
  - Subjects who test positive for Grade 3 or Grade 4 proteinuria or glycosuria that is unexplained or not clinically manageable will be excluded from the study
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Lipid panels (total cholesterol, HDL, direct LDL, and triglycerides). It is recommended that subjects fast for 8 hours prior to the blood draw.
  - HIV testing
    - HIV-1 Ab/Ag
    - HIV-1 RNA by PCR for those subjects who show symptoms consistent with acute infection and who have a negative 4th generation rapid HIV-1 Ab/Ag test or 3rd generation rapid HIV-1 Ab test
    - Any subject with HIV-1 Ab/Ag or an HIV-1 infection (per Appendix 6) is a screen failure and will receive counseling and be referred for appropriate care
  - Hepatitis B testing (HBsAg, HBsAb, HBcAb)
    - If a subject has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed. If the HBV DNA result is positive, the subject is a screen failure.
    - Subjects found to be susceptible to HBV infection should be referred for HBV vaccination
  - Hepatitis C testing
    - If the HCV Ab result is positive, then HCV RNA will be completed unless there is documented evidence that sustained virologic response has been achieved. If the HCV RNA result is positive, the subject is a screen failure

- Computer-assisted self-interview (CASI) for: recent sexual risk events; interest in using PrEP; self-identification of transgender status; education and employment history; and use of tobacco and recreational drugs

- Risk reduction counseling including provision of condoms

6.2.2. Day 1 Visit (Baseline)

Day 1 procedures and randomization may occur as soon as all eligibility criteria are confirmed. The Day 1 visit must occur within 30 days after the Screening visit. The subject must complete all Day 1 procedures before being dispensed study drug. Initiation of treatment with study drug must take place within 24 hours after the Day 1 visit.

- 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test. If test is positive, a retest will be completed. If the retest is positive, the subject will no longer be permitted to participate in the study.

  — A negative HIV-1 RNA by PCR result is required prior to receiving study drug for those subjects who show symptoms consistent with acute infection and who have a negative HIV-1 rapid test

  — Any subject with a positive repeat HIV-1 rapid test or HIV-1 infection (per Appendix 6) will receive counseling and be referred for appropriate care

- Review of adverse events (AEs) and changes in concomitant medications, including assessment of whether STIs were diagnosed and any treatments were received since the Screening visit

- Targeted (symptom directed) physical examination and vital signs (blood pressure, pulse, respiration rate, and temperature) if the Day 1 visit is > 7 days after the Screening visit

- Weight

- CASI for sexual risk events since the last visit

- Randomization in IXRS if all screening assessments meet eligibility criteria

- Drug dispensation

- Adherence and risk reduction counseling including provision of condoms. Subjects will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site immediately for evaluation and HIV-1 testing if they develop such symptoms. Investigator or site support staff must emphasize the importance of the use of barrier protection during the first two weeks from Baseline.

- DXA scan of hip and spine in substudy participants (within 14 days prior to or after the start of treatment)

- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

Throughout the study, subjects may be asked to provide daily information on adherence and sexual risk events through the use of a diary. Participants may also receive periodic contacts to remind them to take their study drug and to provide any additional support needed.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Treatment Assessments Blinded Phase (Weeks 4, 12, and Every 12 Weeks Until the End of Blinded Treatment Phase Visit)

The following evaluations are to be completed at the Weeks 4, 12, and every 12 weeks visits until the End of Blinded Treatment Phase visit unless otherwise specified.

All study visits are to be scheduled relative to the Day 1 visit date. Study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Day 1 visit through Week 12 and study visits thereafter completed within ± 14 days of the protocol-specified visit date through the End of Blinded Treatment Phase visit, unless otherwise specified.

Regularly scheduled evaluations will be performed for all subjects whether or not they continue to receive study drug, unless otherwise specified.

- Targeted (symptom directed) physical examination (**complete physical examination at Weeks 48 and 96 only**)

- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit

- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)

- Weight

- STI testing. Subjects who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the subject at the discretion of the investigator. (Rectal swab not required at Week 4)
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test (**not done for HIV infected subjects**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), CCI
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Lipid panel (total cholesterol, HDL, direct LDL, and triglycerides). Subjects should be instructed to fast (no food or drinks, except water, at least 8 hours prior to blood collection) (**every 24 weeks**)
  - HIV-1 Ab/Ag (**not done for HIV infected subjects**)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

— HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 5) and sample collection for possible genotypic resistance testing for any subjects who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test) or

2) have a positive HIV-1 Ab/Ag test or

3) show symptoms consistent with acute infection regardless of the results of the rapid tests

4) have a recent exposure that is considered high risk for HIV infection

5) have been confirmed HIV infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**every 24 weeks**)

- If a subject has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.
  - Subjects who have tested positive for HBcAb on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 24 weeks
- If the HBsAg or HBV DNA result is positive, the subject will be discontinued and referred to appropriate HBV treatment. If the subject is HIV infected, they may continue participation in the study at the discretion of the investigator.

— Hepatitis C testing (**every 48 weeks**)

- If the HCV Ab result is positive, then HCV RNA will be completed unless there is documented evidence that sustained virologic response has been achieved. If the HCV RNA result is positive, the subject may continue in the study at the discretion of the investigator.
  - Subjects who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks

— Trough PK blood and PBMC sample to evaluate the pharmacokinetics of intracellular TFV-DP and FTC-TP, plasma TFV and FTC. The blood sample should be taken approximately 24 hours after the last dose of study drug and prior to administration of study drug the day of the visit (**Week 4 only**)

— Anytime PK blood sample to evaluate the pharmacokinetics of plasma TFV and FTC (**all visits except Week 4, not done for subjects who have permanently discontinued study drug**)

— DBS collection from blood sample

CCI [redacted]

— CD4, CD8 and CD4/CD8 ratio (**HIV infected subjects only**)

— Large volume blood draw for the following (**HIV infected subjects only. All blood draws will be done at the first study visit upon confirmation of HIV infection, and at the additional timepoints as indicated below. Subsequent draws will be performed at the subjects' regularly scheduled study visit**):

■ Latent and Active Reservoir assessment (**24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

■ T cell response and phenotype (**24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

■ Viral Sequence Diversity assessment (**24 weeks after HIV infection only**)

— Inflammatory/immune activation biomarkers (**HIV infected subjects only. Done at the first study visit upon confirmation of HIV infection, at 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

- CASI for sexual risk events and adherence since the last visit
- Collect and review used and unused study drug for accountability and calculate compliance (**not done for subjects who have permanently discontinued study drug**)
- Drug dispensation (**not done for subjects who have been or will be permanently discontinued from study drug**)
- Adherence and risk reduction counseling including provision of condoms. Subjects will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms. (**Adherence and risk reduction counseling not done for HIV infected subjects.**)
- Subjects may be asked provide daily information on adherence and sexual risk events through the use of a diary
- DXA scan of hip and spine in substudy participants (**Weeks 48 and 96 only**, ± 6 weeks from the protocol-specified visit date) (**not done for subjects who have permanently discontinued study drug**)

6.4. End of Blinded Treatment Phase Visit

Once all subjects have had at least 96 weeks of follow-up after randomization and upon notification by Gilead, all subjects will return to the study center for an End of Blinded Treatment Phase visit (may coincide with their next scheduled study visit).

At the End of Blinded Treatment Phase visit, all subjects will discontinue their blinded study drug and will be given the option to receive F/TAF for 48 weeks in the OL phase. Subjects who have discontinued study drug prior to the end of Blinded Treatment Phase visit due to HIV infection will be eligible to continue participation in the OL phase, but will not be administered F/TAF QD. Subjects who have discontinued study drug for any other reason prior to the End of Blinded Treatment Phase visit will not be eligible to participate in the OL phase.

Subjects who do not participate in the OL phase will discontinue their blinded study drug and will return for a 30-Day Follow-up visit following the End of Blinded Treatment Phase visit.

The following will be performed at the End of Blinded Treatment Phase visit:

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since the last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Subjects who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the subject at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- 4th generation rapid HIV-1 Ag/Ab or 3rd generation rapid HIV-1 Ab test (**not done for HIV infected subjects**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), CCI [redacted]

- Blood sample collection for the following central laboratory analyses:

  — Hematology profile: complete blood count (CBC) with differential and platelet count

  — Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)

  — Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance

  — HIV-1 Ab/Ag (**not done for HIV infected subjects**)

    ■ If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

  — HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 5) and sample collection for possible genotypic resistance testing for any subjects who:

    1) have a positive retest rapid HIV-1 Ab/Ag test (either 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test) or

    2) have a positive HIV-1 Ab/Ag test or

    3) show symptoms consistent with acute infection regardless of the results of the rapid tests

    4) have a recent exposure that is considered high risk for HIV infection

    5) have been confirmed HIV infected

    For details regarding confirmation of HIV infection, please refer to Section 6.11.

  — Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**if > 24 weeks from prior testing**)

    ■ If a subject has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.

      ○ Subjects who have tested positive for HBcAB on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 24 weeks

    ■ If the HBsAg or HBV DNA result is positive, the subject will be discontinued and referred to appropriate HBV treatment. If the subject is HIV infected, they may continue in the study at the discretion of the investigator.

— Hepatitis C testing (**if > than 48 weeks from prior testing**)

  - If the HCV Ab result is positive, then HCV RNA will be completed. If the HCV RNA result is positive, the subject may continue in the study at the discretion of the investigator.

  - Subjects who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks

— Anytime PK blood sample to evaluate the pharmacokinetics of plasma TFV and FTC (**not done for subjects who have permanently discontinued study drug**)

— DBS collection from blood sample

CCI [redacted]

— CD4, CD8 and CD4/CD8 ratio (**HIV infected subjects only**)

— Large volume blood draw for the following (**HIV infected subjects only. All blood draws will be done at the first study visit upon confirmation of HIV infection and at the additional timepoints as indicated below. Subsequent draws will be performed at the subjects' regularly scheduled study visit**):

  - Latent and Active Reservoir assessment (**24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

  - T cell response and phenotype (**24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

  - Viral Sequence Diversity assessment (**24 weeks after HIV infection only**)

— Inflammatory/immune activation biomarkers (**HIV infected subjects only. Done at the first study visit upon confirmation of HIV infection, at 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

- CASI for sexual risk events and adherence since the last visit

- Collect and review used and unused blinded study drug for accountability and calculate compliance (**not done for subjects who have permanently discontinued study drug**)

- OL drug dispensation (**not done for HIV infected subjects**). If the subject has already taken a dose of blinded study drug on the day of the End of Blinded Treatment Phase visit, they should not begin dosing with OL F/TAF until the next day. If the subject has not taken a dose of blinded study drug on the day of the visit, they should take their first dose of OL F/TAF on the same day of the End of Blinded Treatment Phase visit.

- Adherence and risk reduction counseling including provision of condoms. Subjects will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms. (**Adherence and risk reduction counseling not done for HIV infected subjects.**)

- DXA scan of hip and spine in substudy participants (± 6 weeks from the protocol-specified visit date) (**not done for subjects who have permanently discontinued study drug**)

6.5. Treatment Assessments Open-Label Phase (OL Weeks 12, 24, 36, 48, and Every 12 Weeks if Continuing Past OL Week 48)

All study visits in the OL phase are to be scheduled relative to the End of Blinded Treatment Phase visit date. Study visits are to be completed within ± 14 days of the protocol-specified visit date based on the End of Blinded Treatment Phase visit. Subjects participating in the OL phase will return for study visits every 12 weeks for up to 48 weeks.

After subjects in the OL phase of the study have completed 48 weeks of treatment, the study will be considered clinically complete and subjects on OL F/TAF should be transitioned to commercially available drug supplies as applicable. However, subjects in geographic regions where F/TAF is not commercially available for use as PrEP at the completion of the OL phase will be able to continue on F/TAF until F/TAF becomes commercially available, or until Gilead Sciences terminates clinical development of F/TAF for PrEP. These subjects will continue OL study visits every 12 weeks. Subjects in Denmark and the United Kingdom are ineligible for this continued treatment option and must discontinue study drug at the OL Week 48 visit and return 30 days later for a 30 Day Follow-Up visit. Subjects who are HIV infected will discontinue from the study at OL Week 48.

Regularly scheduled evaluations will be made on all subjects, unless otherwise specified.

- Targeted (symptom directed) physical examination (**complete physical examination at OL Week 48 only**)

- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit

- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)

- Weight

- STI testing. Subjects who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the subject at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test (**not done for HIV infected subjects**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), CCI [redacted]
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - Lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) Subjects should be instructed to fast (no food or drinks, except water, at least 8 hours prior to blood collection) (**every 24 weeks**)
  - HIV-1 Ab/Ag (**not done for HIV infected subjects**)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.

— HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 5) and sample collection for possible genotypic resistance testing for any subjects who:

1) have a positive retest rapid HIV-1 Ab/Ag test (either 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test) or

2) have a positive HIV-1 Ab/Ag test or

3) show symptoms consistent with acute infection regardless of the results of the rapid tests

4) have a recent exposure that is considered high risk for HIV infection

5) have been confirmed HIV infected

For details regarding confirmation of HIV infection, please refer to Section 6.11.

— Hepatitis B testing (HBsAg, HBsAb, HBcAb) (**every 24 weeks**)

- If a subject has a negative HBsAg, negative HBsAb, and positive HBcAb, HBV DNA testing will be completed.
  - Subjects who have tested positive for HBcAb on the study during a prior visit do not need to repeat the Hepatitis B testing panel during subsequent visits and instead will have HBV DNA testing performed at visits every 24 weeks
- If the HBsAg or HBV DNA result is positive, the subject will be discontinued and referred to appropriate HBV treatment. If the subject is HIV infected, they may continue in the study at the discretion of the investigator.

— Hepatitis C testing (**every 48 weeks**)

- If the HCV Ab result is positive, then HCV RNA will be completed. If the HCV RNA result is positive, the subject may continue in the study at the discretion of the investigator.
- Subjects who have tested positive for HCV Ab on the study during a prior visit do not need to repeat the HCV Ab test during subsequent visits and instead will have HCV RNA testing performed at visits every 48 weeks

— Anytime PK blood sample to evaluate the pharmacokinetics of plasma TFV and FTC

— DBS collection from blood sample

CCI [redacted]

— CD4, CD8 and CD4/CD8 ratio (**HIV infected subjects only**)

— Large volume blood draw for the following (**HIV infected subjects only. All blood draws will be done at the first study visit upon confirmation of HIV infection, and at the additional timepoints as indicated below. Subsequent draws will be performed at the subjects' regularly scheduled study visit**):

  - Latent and Active Reservoir assessment (**24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)
  - T cell response and phenotype (**24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)
  - Viral Sequence Diversity assessment (**24 weeks after HIV infection only**)

— Inflammatory/immune activation biomarkers (**HIV infected subjects only. Done at the first study visit upon confirmation of HIV infection, at 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter**)

- CASI for sexual risk events and adherence since the last visit
- Collect and review used and unused study drug for accountability and calculate compliance (**not done for HIV infected subjects**)
- Drug dispensation (**not done for HIV infected subjects**)
- Adherence and risk reduction counseling including provision of condoms. Subjects will be educated on the signs and symptoms of acute HIV-1 infection and will be instructed to call and/or present to the site for evaluation and HIV-1 testing if they develop such symptoms. (**Adherence and risk reduction counseling not done for HIV infected subjects.**)
- Subjects may be asked provide daily information on adherence and sexual risk events through the use of a diary
- DXA scan of hip and spine in substudy participants (**OL Week 48 only**, ± 6 weeks from the protocol-specified visit date)

6.6. Unscheduled Visits

Additional unscheduled assessments may be performed at the discretion of the investigator (eg, for evaluation of AEs and/or laboratory abnormalities, including assessment of whether any STIs were diagnosed and any treatments were received since last visit). Subjects who have HIV testing performed during an unscheduled visit will have DBS collection from a blood sample performed.

6.7. Post-Treatment Assessments

6.7.1. Early Study Drug Discontinuation Assessments

If the subject discontinues study drug prior to the OL Week 48 visit, the subject will be asked to return to the clinic within 72 hours of stopping study drug for the Early Study Drug Discontinuation (ESDD) visit. If the subject has not yet had an End of Blinded Treatment Phase visit performed, the subject will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Phase visit, even if the subject discontinues the study drug.

At the ESDD visit, any evaluations showing abnormal results that the Investigator determines to have a possible or probable causal relationship with the study drug, will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Subjects who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the subject at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test (**not done for HIV infected subjects**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.
- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), CCI

- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - HIV-1 Ab/Ag (**not done for HIV infected subjects**)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.
  - HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 5) and sample collection for possible genotypic resistance testing for any subjects who:
    1) have a positive retest rapid HIV-1 Ab/Ag test (either 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test) or
    2) have a positive HIV-1 Ab/Ag test or
    3) show symptoms consistent with acute infection regardless of the results of the rapid tests
    4) have a recent exposure that is considered high risk for HIV infection
    5) have been confirmed HIV infected

    For details regarding confirmation of HIV infection, please refer to Section 6.11.
  - Anytime PK blood sample to evaluate the pharmacokinetics of plasma TFV and FTC
  - CCI [redacted]
  - CD4, CD8 and CD4/CD8 ratio (**HIV infected subjects only**)
  - Large volume blood draw for the following (**HIV infected subjects only. All blood draws will be done at the first study visit upon confirmation of HIV infection**):
    - Latent and Active Reservoir assessment
    - T cell response and phenotype
    - Viral Sequence Diversity assessment
  - Inflammatory/immune activation biomarkers (**HIV infected subjects only**)

- CASI for sexual risk events and adherence since the last visit
- Collect and review used and unused study drug for accountability and calculate compliance
- DXA scan of hip and spine in substudy participants (**if ESDD visit is >12 weeks from previous DXA**)

6.7.2. 30-Day Follow-Up Assessment

All subjects who have received at least one dose of study drug will be required to complete a follow-up visit 30 days (+ 14 days) after discontinuation of the study drug. Subjects who permanently discontinue study drug and continue to attend normal study visits (at minimum one visit at least 30 days after last dose) are not required to complete the follow-up visit.

The following evaluations are to be completed at the 30-Day Follow-Up visit:

At the 30-Day Follow-Up visit, **any evaluations showing abnormal results that the Investigator determines to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained**.

- Targeted (symptom directed) physical examination
- Review of AEs and changes in concomitant medications, including assessment of whether any STIs were diagnosed and any treatments were received since last visit
- When clinically indicated, vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight
- STI testing. Subjects who test positive for any STI will be treated in accordance with local STI guidelines.
  - Genital, rectal, and pharyngeal examination as appropriate
  - Pharyngeal and rectal swabs for gonorrhea and chlamydia (per local lab). Swabs may be self-administered by the subject at the discretion of the investigator.
  - Urine sample for gonorrhea and chlamydia (per central lab)
  - Blood sample for syphilis testing (per local lab)
- 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test (**not done for HIV infected subjects**)
  - If the result for rapid testing is positive, a retest will be completed. If the retest is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.

- Urine collection for urinalysis, urine proteins, urine chemistry (uric acid, phosphate, and creatinine), CCI [redacted]
- Blood sample collection for the following central laboratory analyses:
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance
  - HIV-1 Ab/Ag (**not done for HIV infected subjects**)
    - If the HIV-1 Ab/Ag test is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed as soon as possible.
  - HIV-1 RNA by PCR test (see HIV Testing Algorithm, Appendix 5) and sample collection for possible genotypic resistance testing for any subjects who:
    1) have a positive retest rapid HIV-1 Ab/Ag test (either 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test) or
    2) have a positive HIV-1 Ab/Ag test or
    3) show symptoms consistent with acute infection regardless of the results of the rapid tests
    4) have a recent exposure that is considered high risk for HIV infection
    5) have been confirmed HIV infected

    For details regarding confirmation of HIV infection, please refer to Section 6.11.

CCI [redacted]

  - CD4, CD8 and CD4/CD8 ratio (**HIV infected subjects only**)

6.8. Criteria for Restarting Study Drug After an Interruption

If a subject interrupts study dosing temporarily for more than 14 consecutive days, the subject should have samples collected for the following HIV tests prior to restarting study dosing:

- 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test
  - If the result for rapid HIV testing is positive, a retest will be completed. If the retest is positive, the subject must not restart study drug, and may opt to begin a full HIV treatment regimen until the HIV-1 diagnosis is confirmed, at investigator discretion {Center for Disease Control and Prevention (CDC) 2018}.
  - Upon testing negative for the rapid HIV-1 test, the subject may restart study dosing while pending the central lab HIV tests, at the investigator's discretion.
- HIV-1 Ab/Ag (per central lab)
- HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing (per central lab)

For details regarding confirmation of HIV infection, please refer to Section 6.11.

6.9. Criteria for Discontinuation of Study Treatment

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures until the End of Blinded Treatment Phase visit. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

Study medication will be discontinued as applicable in the following instances:

- HIV-1 infection is confirmed
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason

Study medication may be discontinued as applicable in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator (see Section 6.8 for criteria for restarting study drug after an interruption).
- Subject noncompliance
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

6.10. Bone Evaluations

In a subset of subjects (except in Germany), DXA scans of the hip and spine will be performed throughout the study.

During the blinded phase of the study, all DXA substudy subjects will have scans at Day 1, Week 48, Week 96, and End of Blinded Treatment Phase visits. If continuing in the OL phase of the study, DXA substudy subjects will have a scan at OL Week 48.

The Day 1 scan must be completed ± 14 days from start of treatment. All other scans should be completed ± 6 weeks of the protocol-specified visit date.

DXA substudy subjects who plan to temporarily interrupt study drug for more than 14 days should have the DXA scans performed within 14 days of the last dose of study drug, unless the subject has had scans performed for a Week 48, Week 96, End of Blinded Treatment Phase, or OL Week 48 visit within the past 24 weeks prior to interrupting study drug.

DXA scans will be completed at the ESDD visit if the ESDD visit is > 12 weeks after the previous DXA scan. Subjects who have permanently discontinued study drug will not have DXA scans performed during subsequent study visits.

DXA scans will cover the spine and hip to measure changes in bone mineral density. DXA scan results will be provided to study sites as they become available.

A complete description of the procedures performed for the DXA scans will be provided in a DXA manual.

6.11. HIV Infection

Subjects will be assessed for any recent exposures that the investigator considers high risk for HIV infection at each study visit (including phone contacts and any unscheduled visits) from randomization through the end of study, with HIV testing done as clinically appropriate.

Subjects with results confirming HIV infection (per Appendix 6) will immediately discontinue study drug, receive counseling, and be referred for appropriate care. If the subject's HIV-1 RNA is >400 copies/mL, the stored sample for possible genotypic resistance will be sent for testing. An ESDD visit should also be completed within 72 hours of the subject's last dose of study drug.

Once HIV infection is confirmed (per Appendix 6), all records pertaining to the event including laboratory results, clinic notes, prescribed medications, and other relevant information (including local records and records from other clinics) should be collected and submitted together with the HIV-1 infection questionnaire.

Every attempt should be made to keep the HIV infected subject in the study and to continue to perform the required study-related follow-up and procedures through the OL phase.

6.12. Renal Biomarkers

For all subjects, urine will be collected for selected renal biomarkers, including but not limited to retinol binding protein and beta-2-microglobulin, at all study visits from Day 1 through the OL Week 48 or ESDD visit (if applicable). These samples may be stored by Gilead Sciences for a period of up to 15 years.

6.13. Sample Storage

CCI [redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures performed (eg, elective procedures, surgery, endoscopy, tooth extraction, transfusion). The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.5)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). For specific information on handling of clinical laboratory abnormalities in this study, please refer to Appendix 4.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for Collection Prior to Study Drug Initiation:

Prior treatment history is collected as part of the study entry criteria and evaluation of individual patient characteristics and will not be generating lack of effect reports as this is outside the scope of the present clinical study. However, investigators should report any cases of lack of effect that they feel appropriate regarding the previous treatment regimen as spontaneous reports to the relevant authorities or marketing authorisation holders.

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the electronic case report form (eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable.
Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE eCRF.

Follow-up of adverse events will continue through the last day on study (including the follow-up off-study medication period of the study) and/or until the Investigator and/or Gilead Sciences determine that the subject's condition is stable. Gilead Sciences may request that certain adverse events be followed until resolution.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the SAE information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the SAE on the paper serious adverse event report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

Gilead PVE contact information: Email: PPD
Fax: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the Safety Report eCRF.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Special Situations

Special situation reports include reports of medication error, abuse, misuse, or overdose, occupational exposure with an AE, and reports of adverse reactions associated with product complaints. Medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient or consumer. Abuse is defined as persistent, sporadic or intentional excessive use of a medicinal product by a patient accompanied by harmful, physical, and/or psychological effects. Misuse is defined as any use of a medicinal product in a way that is not in accordance with the protocol instructions or the local prescribing information and may be accompanied by harmful physical and/or psychological effects. An overdose is defined as a dose taken (accidentally or intentionally) exceeding the dose as prescribed by the protocol or the maximal recommended daily dose as stated in the Product Labelling, specifically notated in the Investigator Brochure, (as it applies to the daily dose for the subject/patient in question). Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s) or the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging or distribution of the product.

7.5.1. Reporting Special Situations

Electronic Special Situations Reporting

- Site personnel record all special situations data in the eCRF database and from there transmit the special situations information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If it is not possible to record and submit the special situations information electronically, because the eCRF database cannot be accessed or is not available (including at study start), record the information on the paper special situations report form and submit by e-mail or fax within 24 hours of the investigator's knowledge of the event to:

Gilead PVE contact information:

Email: PPD
Fax: PPD

- As soon as it is possible to do so, any special situations reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

- If any special situations have been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- All special situations data will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Additional information may be requested to ensure the timely completion of accurate special situations reports. Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report eCRF; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be recorded on the AE eCRF.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.5 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4 as outlined below.

- All clinically significant Grade 3 and 4 laboratory abnormalities should be repeated within 3 calendar days to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of investigational medicinal product for any Grade 3 and 4 laboratory abnormality that in the opinion of the Investigator is clinically significant and may pose a risk to the subject's safety.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Appendix 4).

Any questions regarding toxicity management should be directed to the Medical Monitor.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue investigational medicinal product at the discretion of the Investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 3-4 laboratory abnormality (e.g., CK elevation after strenuous exercise, or triglyceride elevation that is nonfasting or that can be medically managed) or a Grade 3-4 clinical event considered unrelated to investigational medicinal product.

7.6.4. Management of Bone Evaluation

As there may be uncertainty surrounding the clinical significance and management of decreases in bone mineral density, Gilead recommends that any subject who has a DXA scan that demonstrates a decrease from baseline of > 5% in the spine region or > 7% in the hip region be followed per local medical standards and as per the discretion of the investigator.

7.6.5. Management of Changes in Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (GFR), according to the Cockcroft-Gault formula, will be followed post-baseline during the study. All subjects with estimated GFR < 60 mL/min must have serum creatinine and subject's weight measured again within 3 calendar days of receipt of results. If a subject has confirmed estimated GFR < 60 mL/min, the investigator should notify the Medical Monitor, evaluate potential causes, re-assess the potential risks and benefits of continued treatment in the study, and consider consultation with a qualified nephrologist.

7.6.6. Potential High-Risk Exposure

For subjects who present after a high-risk sexual exposure and request post-exposure prophylaxis (PEP), investigators may discontinue the subject's study medication and provide PEP in accordance with local medical practice and/or guidelines. Subjects who complete their PEP regimen and wish to continue on study may resume with study medication following the criteria as detailed in Section 6.8.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To assess the rates of HIV-1 infection in men (MSM) and transgender women (TGW) who have sex with men who are administered daily F/TAF or F/TDF with a minimum follow-up of 48 weeks and at least 50% of subjects have 96 weeks of follow-up after randomization

The secondary objectives of this study are:

- To compare bone safety between the treatments as determined by dual energy x-ray absorptiometry (DXA) tests of hip and spine bone mineral density (BMD) in a subset of participants at Week 48 and Week 96 in the blinded phase

- To compare renal safety between the treatments as determined by urine retinol-binding protein (RBP) to creatinine ratio, urine beta-2-microglobulin to creatinine ratio, urine protein to creatinine ratio (UPCR), and serum creatinine at Week 48 and Week 96 in the blinded phase

- To assess the rated of HIV-1 infection in men (MSM) and transgender women (TWG) who have sex with men who are administered daily F/TAF or F/TDF when all subjects have 96 weeks of follow-up after randomization

- To compare the general safety between the treatments

Exploratory objectives of this study include:

[redacted]

8.1.2. Primary Endpoints

The primary endpoint will be the incidence of HIV-1 infection per 100 PY when all subjects have a minimum follow-up of 48 weeks and at least 50% of the subjects have 96 weeks of follow-up after randomization. HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated subjects, or

2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or

3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

Please refer to Appendix 6 for more details.

8.1.3. Secondary Endpoints

The key (α-controlled) secondary endpoints in the blinded phase are (in the following order):

- The percent change from baseline in hip BMD at Week 48 in a subset of subjects
- The percent change from baseline in spine BMD at Week 48 in a subset of subjects
- Assessment of renal biomarkers at Week 48
  - percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - percent change from baseline in urine RBP to creatinine ratio
  - distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 48

Other secondary endpoints include:

- The incidence of HIV-1 infection (as defined in Appendix 6) per 100 PY when all subjects have 96 weeks of follow-up after randomization
- The percent change from baseline in hip and spine BMD at Week 96 in the blinded phase in a subset of subjects

- Assessment of renal biomarkers at Week 96 in the blinded phase
  - — percent change from baseline in urine beta-2-microglobulin to creatinine ratio
  - — percent change from baseline in urine RBP to creatinine ratio
  - — distribution of UP and UPCR categories
- The change from baseline in serum creatinine at Week 96 in the blinded phase
- The incidence of treatment-emergent adverse events and laboratory toxicities

8.1.4. Other Endpoints of Interest

- The intracellular TFV-DP and FTC-TP trough concentrations (C_{trough}) in PBMCs.
- The adherence rate using TFV-DP levels in DBS along with plasma FTC and/or TFV levels
- The incidence of HIV-1 infection per 100 PY at OL Week 48 for those who randomize to the F/TAF arm at baseline
- From the OL phase baseline to OL Week 48, percentage change in hip and spine BMD (in a subset of subjects), assessment of renal biomarkers (percent change in urine beta-2-microglobulin to creatinine ratio and urine RBP to creatinine ratio, distribution of UP and UPCR categories), and change from baseline in serum creatinine for those who switch to F/TAF from F/TDF in the OL phase
- The type and frequency of sexual practices that are associated with increased risk of HIV-1 infection

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Randomized Analysis Set

Subjects that are randomized into the study will be included in this analysis set. This is the primary analysis set for by-subject listings.

8.2.1.2. Full Analysis Set (FAS)

The Full Analysis Set will include all the subjects who randomize and receive at least one dose of study drug. The FAS will exclude subjects with major protocol violations (e.g., HIV-1 positive at baseline). The FAS analysis set is the primary analysis set for the efficacy endpoints.

8.2.1.3. Per Protocol Analysis Set (PP)

The Per-Protocol (PP) analysis set will include all subjects who (1) randomize into the study, (2) receive at least one dose of study drug, and (3) have not committed any major protocol violation, including the violation of key entry criteria.

Subjects meeting any of the following criteria will be excluded from the PP analysis set:

- HIV-1-positive at baseline
- Subjects who meet the exclusion criterion for receiving ongoing therapy with any of the medications listed in the table in protocol Section 5.4 including drugs not to be used with FTC and TAF
- Non-adherence to study drug: subjects with poor adherence rate for active study drug

8.2.1.4. Safety Analysis Set

The primary analysis set for safety analyses is defined as all subjects who randomize in to the study and received at least one dose of study drug.

8.2.1.5. Hip DXA Analysis Set

The Hip DXA analysis set will include all subjects who randomize and receive at least one dose of study drug, had nonmissing hip BMD value for the baseline visit and at least one postbaseline visit. Subjects will be grouped according to the treatment they actually received.

8.2.1.6. Spine DXA Analysis Set

The Spine DXA analysis set will include all subjects who randomize and receive at least one dose of study drug, and had nonmissing spine BMD value for the baseline visit and at least one postbaseline visit. Subjects will be grouped according to the treatment they actually received.

8.2.1.7. PBMC Analysis Set

The PBMC analysis set will include all subjects who randomize and have receive at least one dose of study drug and for whom intracellular TFV-DP levels are available.

8.2.1.8. PK Analysis Set

The PK analysis set will include all subjects who randomize and receive at least one dose of study medication and for whom concentration data of any analytes of interest (eg, TFV and TAF) is available. The PK analysis set will be used for analyses of general pharmacokinetics.

8.3. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity and age.

Baseline data will include a summary of body weight, height and body mass index, number of sexual partners in the last 3 months prior to screening, and number of acts of condomless anal intercourse.

8.4. Efficacy Analysis

8.4.1. Primary Analysis

The primary endpoint will be the incidence of HIV-1 infection per 100 PY (HIV-1 infection defined by the HIV Infection Endpoint Definition in Appendix 6). The timing of the primary analysis will occur when the last subject has a minimum of 48 weeks of follow-up and at least 50% of the subjects have 96 weeks of follow-up after randomization. The primary analysis will consist of a non-inferiority evaluation of F/TAF versus F/TDF, with respect to the HIV-1 infection rate in PY as determined by rate ratios. It will be concluded that F/TAF is non-inferior to F/TDF if the upper bound of the 95% confidence interval of the rate ratio (F/TAF divided by F/TDF) is less than 1.62 using a generalized model associated with a Poisson distribution and logarithmic link with the treatment group being the covariate.

If non-inferiority of F/TAF is established to F/TDF, and the upper bound of the 95% CI is less than 1, then superiority of F/TAF over F/TDF will be established.

8.4.2. Secondary Efficacy Analysis

A similar analysis to the primary analysis, when all subjects have 96 weeks of follow-up after randomization will be conducted. Similar incidence rates and confidence intervals will be reported for the extended follow up time.

8.5. Safety Analysis

All safety analyses will be performed using the safety analysis set.

All safety data collected on or after the date that study medication was first dispensed up to the date of last dose of study medication plus 30 days will be summarized by treatment group. Data for the pretreatment and treatment-free follow-up period will be included in data listings.

8.5.1. Extent of Exposure

A subject's extent of exposure to study medication will be generated from the study medication administration data. Exposure data will be summarized by treatment group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration. Dosing information for individual subjects will be listed.

8.5.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. Adverse events meeting the following criteria are defined as treatment-emergent AEs:

- Events with onset dates on or after the first dose date of study drug, and no later than 30 days after the study drug stop date, and/or
- Events that result in premature permanent study medication discontinuation

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study medication, and effect on study drug dosing.

8.5.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Absolute values and changes from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the GSI Grading Scale for severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to the date of last dose of study medication plus 30 days, will be summarized. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent. The maximum toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study medication or after the subject has been discontinued from treatment plus 30 days will be included in a data listing.

8.5.4. Bone Mineral Density

Percentage change from baseline in observed hip and spine BMD will be summarized for subjects participating in the DXA sub-study. The difference in percentage change at Week 48 from baseline between the two treatment arms will be tested using ANOVA.

In addition, missing values for BMD will be imputed using LOCF method and analyzed similarly. Similar methods will be used to analyze these endpoints at Week 96 of the blinded phase.

8.5.5. Renal Biomarkers

The percent changes from baseline in observed renal biomarkers of urine beta-2-microglobulin to creatinine ratio and urine RBP to creatinine ratio at Week 48 will be summarized using descriptive statistics. The difference in percent changes from baseline between two treatment arms will be tested using Wilcoxon rank sum test.

The distribution of the UP and UPCR categories at Week 48 will be compared between the 2 treatment groups adjusting for baseline categories using rank analysis of covariance.

The change from baseline in serum creatinine at Week 48 will be summarized using descriptive statistics. The difference in change from baseline between two treatment arms will be tested using ANOVA model.

In addition, missing values for renal biomarkers will be imputed using LOCF method and analyzed similarly. Similar methods will be used to analyze these endpoints at Week 96 of the blinded phase.

8.5.6. Other Safety Evaluations

Weight will be summarized by visit.

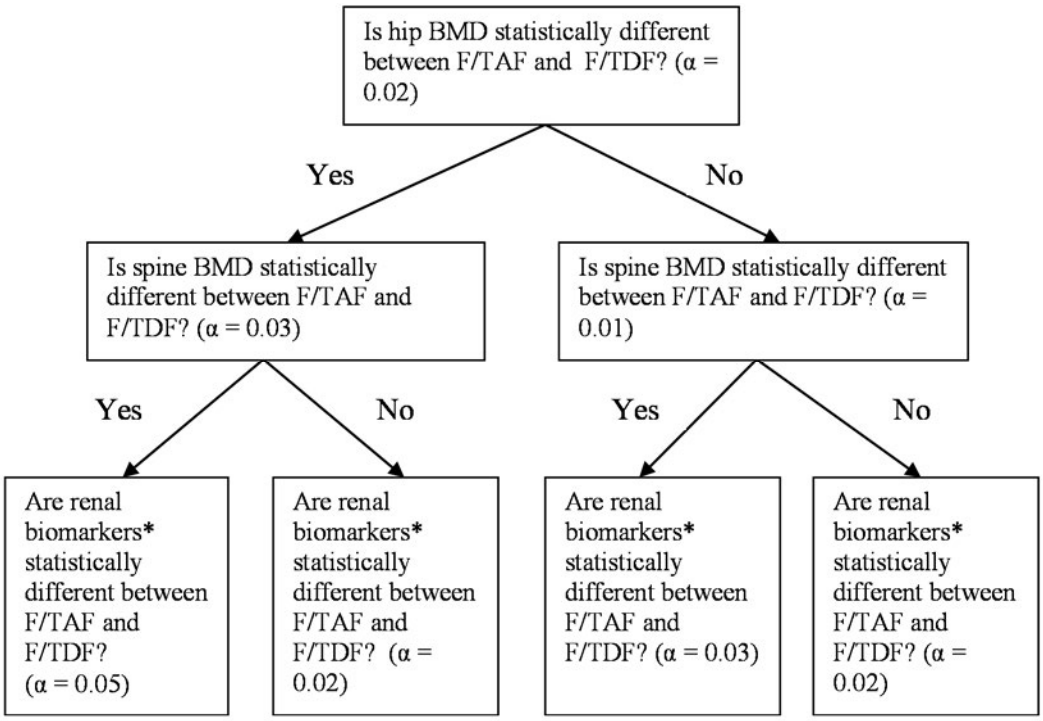
8.6. Statistical Testing Procedure

The primary hypothesis of non-inferiority of F/TAF relative to F/TDF, with respect to the incidence of HIV-1 infection rate per 100 PY will be tested first. Non-inferiority test will be performed at one-sided, 0.025 alpha level. Multiplicity adjustments for safety endpoints will be performed at Week 48 of the blinded phase with a fallback procedure {Wiens 2005} in the sequential order given below with pre-specified two-sided alpha levels:

a) Hip BMD (alpha = 0.02)

b) Spine BMD (alpha = 0.01)

c) Renal biomarkers (alpha = 0.02)



* Renal biomarkers will be tested sequentially as follows: urine beta-2-microglobulin to creatinine ratio, urine RBP to creatinine ratio, distribution of UP and UPCR categories and serum creatinine.

8.7. Pharmacokinetic Analysis

The PK of intracellular TFV-DP and FTC-TP C_{trough} in PBMCs will be summarized using descriptive statistics. Additionally, the population PK of TAF, TFV, and/or FTC may be explored.

8.8. Sample Size

A sample size of 2500 in each arm (1:1 randomization) provides at least 82% power to show F/TAF is non-inferior to F/TDF with respect to the HIV-1 infection rate. In this power analysis, a HIV-1 infection rate of 1.44 per 100 PY in the F/TAF and F/TDF treatment arms, a 2-sided Type 1 error rate of 5%, a non-inferiority margin of 1.62, and an average follow-up of 2 years are assumed.

The non-inferiority (NI) margin of 1.62 and HIV-1 infection rate of 1.44 per 100 PY are based on an equal weighting approach using three historical studies of F/TDF versus placebo/untreated arms in MSM populations that are very similar to the population intended for this study (see Table 8-1 below; the NI margin of 1.62 per 100 PY is the square-root of the lower bound of the 95% CI (2.64) of rate ratio to preserve 50% of treatment effect). The largest of the three studies is the IPREX study and the unprotected receptive anal intercourse (URAI) subgroup of the IPREX study is a high-risk population similar to the intended population of this study. Equal weighting for the three studies gives relatively more weight to the two smaller contemporary studies (PROUD and IPERGAY) than the alternative method of inverse variance

weighting, thus providing an estimate that is likely to be closer to the true estimate of F/TDF efficacy for PrEP. PROUD and IPERGAY were conducted when F/TDF was already established as an effective PrEP medication and represent the status for subjects in the proposed study. IPREX, the largest and earliest of these three studies, was conducted when the effectiveness of F/TDF for PrEP was not established; thus, patients were informed of the unproven efficacy of F/TDF, which likely contributed to the much lower adherence rate in the IPREX trial. In contrast, PROUD and IPERGAY are more recent studies and were conducted after F/TDF was approved for prevention of HIV in a similar risk population, and likely contributed to the much higher adherence rate reported.

Table 8-1. Efficacy Information from Truvada as PrEP in MSMs

Clinical Trial	Sample Size Placebo (PY Follow-Up)	Sample Size F/TDF (PY Follow-Up)	HIV Infections (Incidence per 100 PY [95% CI])		Rate Ratios in HIV Infection Rates, per 100 PY [95% CI]	Enrolment
			PBO	F/TDF		
IPREX (URAI subgroup) at screening	753 (1054)	732 (1055)	56 (5.3) [4.0, 6.8]	23 (2.2) [1.4, 3.2]	2.4 [1.5, 3.9]	July 10, 2007 - Dec 17, 2009
PROUD	255 (222)	268 (243)	20 (9.0) [5.6, 13.4]	3 (1.2) [0.3, 3.5]	7.3 [2.2, 24.2]	Nov 29, 2012 – Apr 30, 2014
IPERGAY	201 (212)	199 (220)	14 (6.6) [3.9, 10.6]	2 (0.9) [0.2, 3.2]	7.3 [1.7, 31.6]	Feb 22, 2012 – Oct 23, 2014
Pool	1209 (1488)	1199 (1518)	90 (6.0) [4.9, 7.5] {6.96}*	28 (1.9) [1.3, 2.6] {**1.44**}*	5.1* [**2.64**, 9.70]	

Source: iPrEX from {Grant 2010}; Ipergay from {Molina 2015}; PROUD from {McCormack 2015}
* The pooled incidence rate for placebo and F/TDF, based on equal weighting of three studies, are within {} which are used for estimating the rate ratio and its 95% CI. .

The DXA substudy with 400 subjects (200 in each treatment group) will provide at least 95% power to detect 1.54% difference between F/TAF and F/TDF treatment groups in terms of percentage change from baseline to Week 48 in BMD. In this power assessment, it is assumed that the standard deviation for percent change in BMD is 3.05% and 3.15% in the F/TAF and F/TDF treatment groups, respectively and 2 sided t-test will be conducted at 0.01 level. The mean differences and standard deviations are based on Studies GS-US-292-0104/ GS-US-292-0111 (E/C/F/TAF vs E/C/F/TDF) and HBV Studies GS-US-320-0108/ GS-US-320-0110 (TAF vs TDF). To be conservative, the smallest effect size from spine in HIV studies was used for the estimation of mean difference and standard deviation between the 2 treatments in the sample size calculation.

For the percent change in renal biomarkers of urine beta 2-microglobulin to creatinine ratio and urine RBP to creatinine ratio from baseline to Week 48, the sample size of 2500 in each arm will have at least 95% power, given the probability of a subject from F/TAF is less than that from F/TDF, P(F/TAF < F/TDF), is at least 55% using a 2 sided Wilcoxon rank sum test at 0.02 level.

The sample size of 2500 in each arm will also provide at least 95% power to demonstrate that F/TAF has 0.014 mg/dL less increase at Week 48 in serum creatinine than F/TDF, assuming the standard deviation is 0.114 and 0.097 in F/TAF and F/TDF, respectively, and 2 sided t-test will be conducted at 0.02 level. The mean differences and standard deviations are based on Gilead HIV Studies GS-US-292-0104/GS-US-292-0111 (E/C/F/TAF vs E/C/F/TDF) and HBV Studies GS-US-320-0108/GS-US-320-0110 (TAF vs TDF). To be conservative, the smaller effect size from HBV Studies GS-US-320-0108/GS-US-320-0110 was used for the estimation of mean difference and standard deviation between the 2 treatments in the sample size calculation.

The above power calculations for BMD and renal biomarkers are based on historical data from studies where patients take study drug daily, if patients are less than fully adherent, the observed benefit of F/TAF compared to F/TDF will be less than these historical estimates, and thus the above power calculation may be overly optimistic.

8.9. Data Monitoring Committee

An independent data monitoring committee (IDMC) will be convened to primarily evaluate the safety of the treatments in this population. There are no a priori plans to stop for efficacy or futility with formal boundaries. At a minimum, the IDMC will include two clinicians (including a chair person), a biostatistician, a prevention expert, and a community member. The initial evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 24 (or prematurely discontinued from the study drug) or (2) after 50 HIV-1 infection events have been reported, whichever occurs earlier. The second evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 48 (or prematurely discontinued from the study drug) or (2) after 100 HIV-1 infection events have been reported, whichever occurs earlier. The third evaluation by the IDMC will occur either (1) after 50% of participants have completed Week 72 (or prematurely discontinued from the study drug) or (2) after 150 HIV-1 infection events have been reported, whichever occurs earlier. Other specifics regarding roles and responsibilities will be described in the IDMC charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions
NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e. history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e. United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

The study monitor will provide instructions for return to the designated disposal site. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs or IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met: the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Emtricitabine and Tenofovir Alafenamide (F/TAF) Fixed-Dose Combination Once Daily for Pre-Exposure Prophylaxis in Men and Transgender Women Who Have Sex with Men and Are At Risk of HIV-1 Infection

GS-US-412-2055, Amendment 5, 05 September 2018

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Scott McCallister, MD (Printed)
Medical Monitor

PPD

Signature

4 Sep 18

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

			Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
Study Procedure	**Screening**	**Day 1**	**4**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**Every 12 Weeks**	**End of Blinded Treatment Phase Visit[b]**	**12**	**24**	**36**	**48**	**Every 12 Weeks[d]**	**30 Day Follow-up[e]**	**ESDD[f]**
Informed Consent	X																			
Medical History	X																			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X						X				X						X			
Targeted Physical Exam		X[o]	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X
Vital Signs[g]	X	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Genital, Rectal, and Pharyngeal Examination for STIs as appropriate	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharyngeal Swab for Gonorrhea and Chlamydia[ac] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rectal Swab for Gonorrhea and Chlamydia (Local Laboratory)[ac]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample for Gonorrhea and Chlamydia	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Rapid HIV-1 Ag/Ab Test (In-Clinic)[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Ab/Ag[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 RNA by PCR[r]	X	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

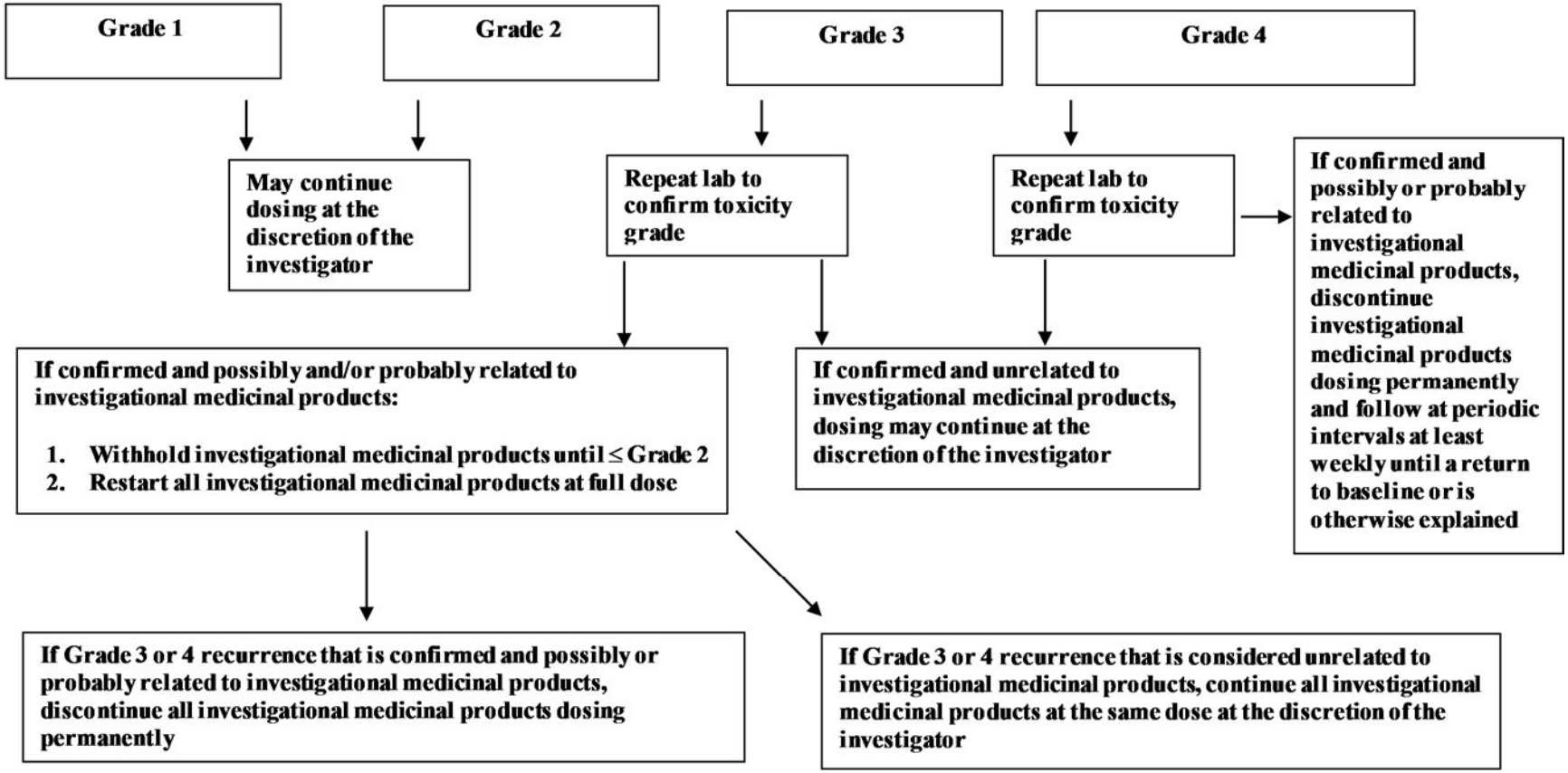
			Double-Blind Treatment End of Week[a]									Post Week 96	Open-Label Treatment End of Week[c]							
Study Procedure	**Screening**	**Day 1**	**4**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**Every 12 Weeks**	**End of Blinded Treatment Phase Visit[b]**	**12**	**24**	**36**	**48**	**Every 12 Weeks[d]**	**30 Day Follow-up[e]**	**ESDD[f]**
Dipstick Urinalysis (In-Clinic)	X																			
Urinalysis, Urine Protein, Urine Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI																				
Blood Sample for Chemistry Profile[h]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sample for Hematology Profile[i]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DBS[j]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood Sample for Syphilis testing[k] (Local Laboratory)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B Testing (HBsAg/HBsAb/HBcAb)	X				X		X		X		X	X[ad]	X[ad]		X		X	X[ad]		
Hepatitis C Testing (HCV Ab)	X						X				X	X[ae]	X[ae]				X	X[ae]		
Estimated GFR	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids (fasting not required at screening)	X				X		X		X		X	X[t]			X		X	X[t]		
Trough PK blood sample (PBMC and plasma)[l]			X																	
Anytime PK blood sample (plasma only)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
CCI																				
CASI Questionnaire[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Randomization in IXRS		X																		

Study Procedure	Screening	Day 1	Double-Blind Treatment End of Week[a] 4	12	24	36	48	60	72	84	96	Post Week 96 Every 12 Weeks	Open-Label Treatment End of Week[c] End of Blinded Treatment Phase Visit[b]	12	24	36	48	Every 12 Weeks[d]	30 Day Follow-up[e]	ESDD[f]
Risk Reduction/ Adherence Counseling	X[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
DXA Scan (Hip and Spine)		X[v]					X[w]				X[w]		X[w]				X[w]			X[x]
Study Drug Dispensation and Accountability		X[y]	X	X	X	X	X	X	X	X	X	X	X[z]	X	X	X	X[aa]	X		X[ab]
CD4, CD8, and CD4/CD8 (HIV Infected Only)			Performed at all visits after HIV infection.																X	X
Latent and Active Reservoir assessment (HIV Infected Only)			Performed for HIV infected subjects only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X
T cell response and phenotype (HIV Infected Only)			Performed for HIV infected subjects only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X
Viral Sequence Diversity assessment (HIV Infected Only)			Performed for HIV infected subjects only. Performed at first study visit after HIV infection and at regularly scheduled study visit 24 weeks after HIV infection only.																	X
Inflammatory/Immune Activation Biomarkers (HIV Infected Only)			Performed for HIV infected subjects only. Performed at first study visit after HIV infection and at regularly scheduled study visits 24 weeks and 48 weeks after HIV infection, and every 48 weeks thereafter.																	X

a All study visits in the double-blind phase are to be scheduled relative to the Day 1 visit date. Visit windows are ± 2 days of the protocol-specified date through Week 12, ± 14 days of the protocol-specified date through the End of Blinded Treatment Phase visit, unless otherwise specified.
b End of Blinded Treatment Phase visit to occur after all subjects reach Week 96.
c Study visits are to be completed within ± 14 days of the protocol-specified visit date based on the End of Blinded Treatment Phase visit.
d Subjects will continue study visits every 12 weeks until study drug F/TAF is commercially available in their region (except Denmark and the United Kingdom)
e Must be completed 30 days after discontinuing study drug. **All subjects who have received at least one dose of study drug will be required to complete a follow-up visit**. For the purpose of scheduling a 30 Day Follow-Up visit, a ± 14 days window may be used.
f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the End of Blinded Treatment Phase visit.
g Vital signs measurement including blood pressure, pulse, respiration rate, and temperature. After the Day 1 visit, vital signs completed when clinically indicated.
h Chemistry profile: alkaline phosphatase, AST, ALT, GGT, total bilirubin, direct and indirect bilirubin, total protein, albumin, LDH, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN).

i Complete blood count (CBC) with differential and platelet count
j Blood sample collected for DBS testing to be stored at central laboratory
k Local STI testing for syphilis.
l Trough PK blood samples to evaluate the pharmacokinetics of intracellular TFV-DP and FTC-TP, plasma TFV and FTC. The blood sample should be taken approximately 24 hours after the last dose of study drug and prior to administration of study drug the day of the visit
[redacted]
n Computer-assisted self-interview (CASI)
o If Day 1 is completed > 7 days after the screening visit
p 4th generation rapid HIV-1 Ab/Ag or 3rd generation rapid HIV-1 Ab test may be used. If 4th generation rapid HIV-1 Ag/Ab or 3rd generation rapid HIV-1 Ab test is positive, a retest will be completed. At Screening or Day 1, if rapid retest is positive the subject is a screen failure. At all other visits if rapid retest is positive, then HIV-1 RNA by PCR test and sample collection for possible genotypic testing will be completed.
q At Screening, if HIV-1 Ab/Ag is positive the subject is a screen failure. At all other visits if HIV-1 Ab/Ag is positive, then HIV-1 RNA by PCR test and sample collection for possible genotypic testing will be completed.
r At Screening or Day 1, if the subject has a negative rapid test, but has signs or symptoms of acute HIV-1 infection, an HIV-1 RNA by PCR test will be completed and if HIV-1 RNA by PCR is positive, subject cannot participate in the study. At all other visits, HIV-1 RNA by PCR and sample collection for possible genotypic resistance testing will be completed for any subjects who (1) have a positive retest rapid HIV-1 Ab/Ag test or (2) have a positive HIV-1 Ab/Ag test or (3) show symptoms consistent with acute infection regardless of the results of the rapid tests, (4) have a recent exposure that is considered high risk for HIV infection, or (5) have been confirmed HIV infected. If HIV infection is confirmed, subject will discontinue study drug immediately and should return for an ESDD visit within 72 hours. The subject will receive counseling and be referred for appropriate care. If viral load > 400 copies/mL the collected sample will be sent for genotypic resistance testing.
s At Day 1, HIV-1 RNA by PCR and sample collection for possible genotypic testing will be completed for any subjects who show symptoms consistent with acute HIV-1 infection regardless of the results of the rapid tests.
t Every 24 Weeks only
u Only risk reduction counseling at Screening
v DXA scans of hip and spine in substudy participants (within 14 days prior to or after the start of treatment)
w DXA scans are to be scheduled ± 6 weeks to the protocol-specified dates for the Week 48, Week 96, End of Blinded Treatment Phase, and OL Week 48 visits.
x DXA scan of hip and spine in substudy participants (if discontinuation is > than 12 weeks from the prior DXA scan)
y Only study drug dispensation at Day 1
z OL drug dispensation (all eligible subjects will receive F/TAF)
aa Study drug dispensing: No study drug dispensation at OL WK 48 except for subjects continuing on past OL WK 48 due to commercial drug unavailability.
ab No study drug dispensed.
ac Swabs may be self-administered by the subject at the discretion of the investigator.
ad Hepatitis B testing (HBsAg, HBsAb, HBcAb) to be completed every 24 weeks. Hepatitis B testing to be completed at the End of Blinded Treatment Phase visit if > than 24 weeks from prior testing.
ae Hepatitis C testing (HCV Ab) to be completed every 48 weeks. Hepatitis C testing to be completed at the End of Blinded Treatment Phase visit if > than 48 weeks from prior testing.

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale Version: 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, ≥ 7 Months**[#]	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	>ULN to 150 mEq/L >ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year** 3.0 to <LLN mmol/L **Infant <1 Year** 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	3.0 to <LLN mEq/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year** 5.6 to 6.0 mmol/L **Infant <1 Year** >ULN to 6.0 mEq/L >ULN to 6.0 mmol/L	5.6 to 6.0 mEq/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L > 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** 55 to 64 mg/dL 3.03 to 3.58 mmol/L **Infant, < 1 Month** 50 to 54 mg/dL 2.8 to 3.0 mmol/L		40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥2 Years**	7.8 <LLN mg/dL 1.94 to <LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥7 days -2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to <7.8 mg/dL 1.74 to <1.94 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant, < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1 Year–14 Years	3.0 to <LLN mg/dL 0.96 to <LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to <LLN mg/dL 1.12 to <LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine**	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years** **Pediatric < 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN NA	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L 11.0 mEq/Lto <LLN 11.0 mmol/L to <LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L 8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L < 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting) **Adult** LDL (Fasting) **Pediatric >2 to <18 years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L >130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L > 190 mg/dL >4.92 mmol/L	NA NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects > 70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatrics <16 years** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below				
Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	>999 to 1999 mg/24 h	>1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Mo to < 10 Years	201 to 499 mg/m^2/24 h	>499 to 799 mg/m^2/24 h	>799 to 1000 mg/m^2/24 h	> 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

- Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional- symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak-ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

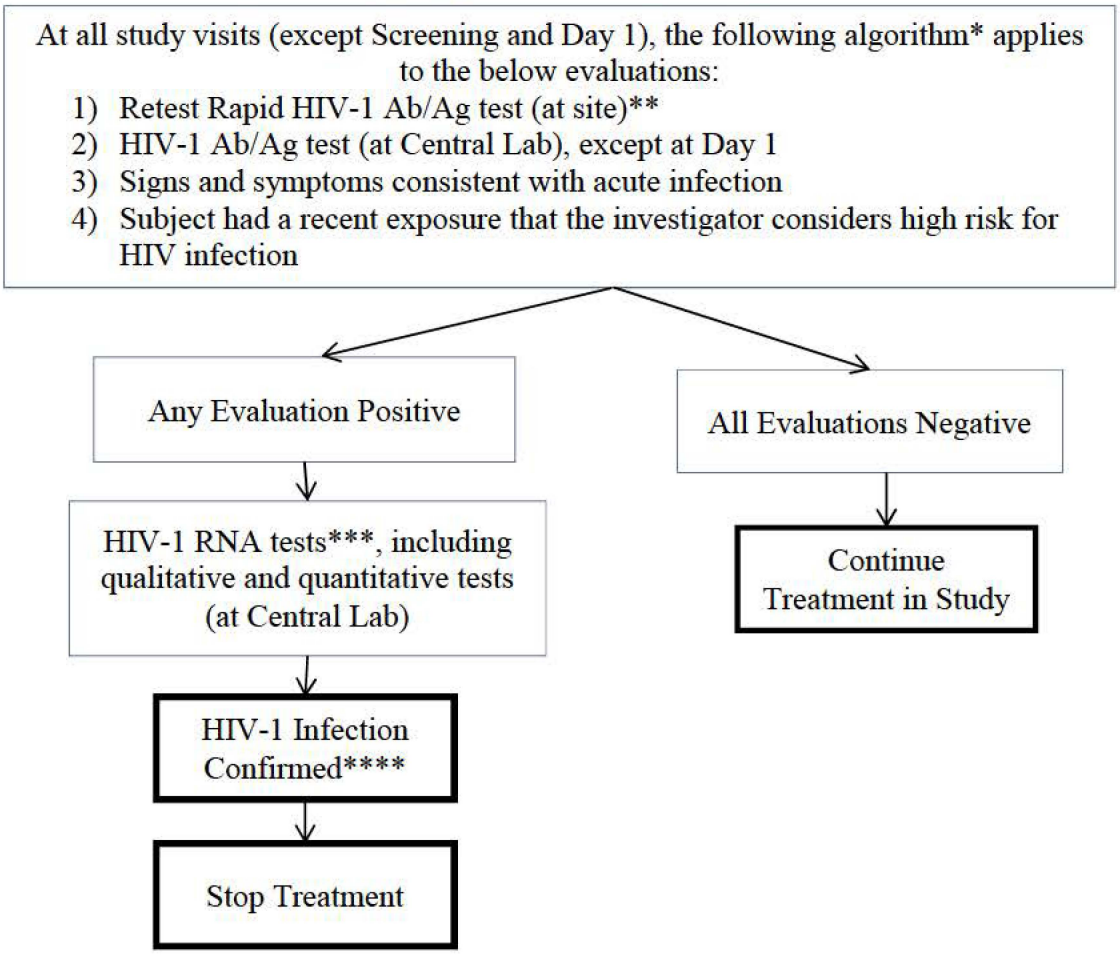
ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 5. HIV Testing Algorithm



* The HIV testing algorithm does not apply to HIV infected subjects.

** If the result for rapid testing is positive, a retest will be completed. If the retest rapid is positive, an HIV-1 RNA by PCR test and sample collection for possible genotypic resistance testing will be completed.

*** May continue study drug, or may begin a full HIV treatment regimen until HIV-1 diagnosis is confirmed, at investigator discretion {Center for Disease Control and Prevention (CDC) 2018}.

**** HIV infection as defined per Appendix 6.

Appendix 6. HIV Infection Endpoint Definition

HIV-1 infection is defined by one or more of the following criteria of contributing HIV tests performed via central lab or local lab:

1) Serologic evidence of seroconversion (reactive screening HIV Antigen/Antibody or Antibody test, confirmed by reactive HIV-1/HIV-2 differentiation assay), excluding HIV vaccinated subjects, or

2) Virologic evidence of HIV-1 infection (positive qualitative HIV-1 RNA test or any detectable quantitative HIV-1 RNA test), or

3) Evidence of acute HIV-1 infection (reactive p24 Antigen or positive qualitative or quantitative RNA, in the absence of reactive HIV-1 Antibody results)

Please refer to the flowchart below which focuses on contributions from the central laboratory and provides a general assessment of contributing HIV tests performed by the central laboratory.